Accumulation of Hospital Days Among Antipsychotic Initiators With Alzheimer’s Disease

Marjaana Koponen PhD\(^a,b,*\), Piia Lavikainen PhD\(^a,b\), Heidi Taipale PhD\(^a,b,c,d\), Antti Tanskanen Phil Lic\(^c,d,e\), Jari Tiikonen MD, PhD\(^c,d\), Sirpa Hartikainen MD, PhD\(^a,b\), Anna-Maija Tolppanen PhD\(^a,b\)

\(^a\) Kuopio Research Center of Geriatric Care, University of Eastern Finland, Kuopio, Finland
\(^b\) School of Pharmacy, University of Eastern Finland, Kuopio, Finland
\(^c\) Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
\(^d\) Department of Forensic Psychiatry, Niuvanniemi Hospital, University of Eastern Finland, Kuopio, Finland
\(^e\) Impact Assessment Unit, National Institute for Health and Welfare, Helsinki, Finland

Keywords:
- Cohort studies
- Hospitalization
- Patient safety
- Alzheimer’s disease
- Antipsychotics

ABSTRACT

Objectives: To compare the accumulation of hospital days, a proposed proxy for overall drug safety, between antipsychotic initiators and noninitiators with Alzheimer’s disease (AD).

Design: Nationwide exposure-matched cohort.

Setting and Participants: Finnish community dwellers who received an incident AD diagnosis in 2005–2011 (n = 70,718). For each antipsychotic initiator, 1 noninitiator was matched on age, sex, and time since AD diagnosis (n = 19,909 matched pairs).

Measures: Accumulation of hospital days was measured during a 2-year follow-up from the national hospital discharge register. Antipsychotic use was ascertained from the National Prescription Register. Association between antipsychotic initiation and accumulation of hospital days was analyzed using negative binomial model.

Results: During the 2-year follow-up, antipsychotic initiators were hospitalized on average for 52.5 (standard deviation 97.7) days and matched noninitiators for 34.7 (standard deviation 72.4) days. Of antipsychotic initiators 23.8% and of noninitiators, 34.1% did not have any hospital days. Antipsychotic initiators had 53% more hospital days (adjusted incidence rate ratio 1.53; 95% confidence interval 1.47–1.59) than noninitiators. Strongest associations were observed during the first 6 months. Antipsychotic initiators had more hospital days with primary diagnosis codes of dementia; mental and behavioral disorders; factors influencing health status; diseases of the respiratory, genitourinary, and circulatory system; certain infectious and parasitic diseases; and symptoms not elsewhere classified, than noninitiators.

Conclusions and implications: Antipsychotic initiators accumulated more hospital days than noninitiators, especially within the first 6 months after initiation. This may indicate adverse events or difficulties in treating the most severe behavioral and psychological symptoms of dementia and health problems triggering them. After initiating antipsychotics, careful and regular monitoring is needed to assess response and decrease the risk of adverse effects and events.

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* Address correspondence to Marjaana Koponen, PhD, School of Pharmacy, University of Eastern Finland, PO Box 1627, FI-70211 Kuopio, Finland.

E-mail address: marjaana.koponen@uef.fi (M. Koponen).

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Antipsychotics are associated with several serious adverse events such as hip fracture, stroke, myocardial infarction, pneumonia, and mortality among older people in general and among persons with dementia. \(^\text{1-9}\) Few previous studies have reported the association between antipsychotic use and hospitalization among older people. \(^\text{10-11}\) All-cause hospitalization is considered as a proxy of overall drug safety. \(^\text{12}\) A Swedish nationwide register-based case-control study found antipsychotics were the psychotropic drug group most strongly related to unplanned hospitalization for any cause among persons age ≥65 years. \(^\text{13}\) Similarly, in a case-time-control study, antipsychotic use was associated with unplanned hospitalizations in both persons age <65 and ≥65 years. \(^\text{14}\) Previous studies have not investigated the risk of hospitalization among persons with Alzheimer’s disease (AD) nor the accumulation of hospital days associated with antipsychotic use, although antipsychotics are commonly used in this group. \(^\text{15}\)

The aim was to investigate whether antipsychotic initiation is associated with accumulation of hospital days among community dwellers with AD and compare the accumulation of hospital days between the most commonly used antipsychotics, risperidone and quetiapine, during a 2-year follow-up.

**Methods**

This study was based on a nationwide register-based MEDALZ (Medication use and Alzheimer’s disease) cohort of all residents of Finland who were newly diagnosed with AD during 2005–2011 and were community-dwelling at the time of AD diagnosis (\(N = 70,718\)). They were identified from the Special Reimbursement Register maintained by the Social Insurance Institution of Finland (SII). The SII grants reimbursement for anti-dementia drugs if predefined diagnostic criteria, based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) \(^\text{16}\) and Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-IV) criteria \(^\text{17}\) for AD, are met. These include exclusion of alternative diagnoses, computed tomography or magnetic resonance imaging scan, symptoms consistent with AD, and confirmation of diagnosis by geriatrician or neurologist. Detailed cohort description has been published previously. \(^\text{18}\)

Data on reimbursed prescription drug purchases during 1995–2015 were extracted from the Finnish Prescription Register. Drugs are classified according to Anatomical Therapeutic Chemical (ATC) classification system. \(^\text{19}\) Antipsychotics were defined as ATC-class N05 A, excluding lithium (N05AN01) and prochlorperazine (N05AB04). Exposure periods were calculated from drug purchases with validated prescriptions drug purchases to drug use periods (PRE2DUP) modeling method. \(^\text{18-20}\) This mathematical modeling method calculates sliding averages of daily dose for each person and each drug from individual purchase histories. The method joins purchases to the same continuous drug use period if the purchased amount is enough to last to the next purchase with personal temporal daily dose, accounting for stocking, personal purchase regularity, and stays at hospital or public nursing home care when drug use is not recorded in the register. Overlapping use periods of individual antipsychotics were combined to the use of “any antipsychotics.”

**Outcome**

All-cause hospitalizations were extracted from the Finnish Care Register for Health Care, which contains the dates of each hospital visit and International Classification of Diseases 10th Revision (ICD-10) codes for discharge diagnoses. The primary outcome was the accumulated number of hospital days during the 2-year follow-up. Secondary outcomes were accumulated numbers of hospital days in general or specialized healthcare, based on the attending physician’s judgement on the specialty that was most relevant for the care of the patient. To assess the reasons for accumulation, hospital days were classified based on the primary discharge diagnosis according to the chapters of the International Statistical Classification of Diseases and Related Health Problems 10th Revision \(^\text{21}\) with few modifications (Supplementary Table 1).

**Formation of Study Sample**

Altogether, 25,788 of the MEDALZ cohort members initiated antipsychotic use between AD diagnosis and December 31, 2013 and were included in this study (Figure 1). Prevalent users were identified with 1-year washout period preceding the initiation date and excluded to avoid prevalent user bias. Because the Prescription Register does not cover drugs used in hospitals, persons who were hospitalized for over 50% of the washout period or had an ongoing hospital stay of ≥3 months at the end of the washout period were excluded. Persons with history of schizophrenia, schizotypal and delusional disorders or bipolar disorder at least 5 years before the AD diagnosis were excluded to focus on antipsychotic use for behavioral and psychological symptoms of dementia (BPSD). The 5-year gap before the AD diagnosis was applied because persons with prodromal symptoms of AD may be misdiagnosed with psychiatric disorders. \(^\text{22}\) To avoid indication bias resulting from antipsychotic use in the treatment of cancer-related nausea, persons with hospital-based diagnoses of cancer or antineoplastic drug use during the year preceding the initiation of antipsychotic use were excluded. At the date of antipsychotic initiation, 1 matched noninitiator was identified for each initiator using incidence density sampling without replacement. Matching criteria were time since AD diagnosis (±90 days), age (±2 years), and sex. The date of antipsychotic initiation of the corresponding case was the index date for the matched noninitiator. The same washout period and exclusion criteria were applied for the noninitiators. Antipsychotic initiators without matched noninitiators were excluded (\(n = 183\)).

**Statistical Analyses**

In the primary analyses, the accumulation of hospital days between initiators and noninitiators was compared for a 2-year follow-up period starting from the index date. In the secondary analyses, the accumulation of hospital days was compared between the users of the 2 most frequently prescribed antipsychotics: quetiapine and risperidone. Negative binomial model was used to calculate the incidence rate ratios (IRR) for the difference in accumulated number of hospital days. Unequal follow-up times truncated because of death and/or changes in antipsychotic use were accounted for by adjusting for log (person-time) in the models. In the main analysis intention-to-treat (ITT) approach was used and the follow-up was censored at the first occurrence of the following: death, 2 years since the index date, or the end of administrative study period (December 31, 2015).

The following 2 sensitivity analyses were conducted to take better account of possible changes in antipsychotic use: (1) the ITT approach with shortened follow-up (180 days after the index date); and (2) the as-treated approach with 2 years of follow-up as in the main analysis. In as-treated approach, follow-up was censored if the initiator discontinued use or if the noninitiator started using antipsychotics. In the as-treated sensitivity analyses comparing quetiapine to risperidone initiators, the follow-up was also censored if person switched to another antipsychotic or started using ≥2 drugs concomitantly. All
analyses were adjusted for age, sex, time since diagnosis of AD, cardiovascular disease, asthma or chronic obstructive pulmonary disease, diabetes, history of stroke and hip fracture, use of benzodiazepines and related drugs, antidepressants and opioids, total number of drugs (other than psychotropics), and total number of hospital days in the year preceding the index date. Definitions of covariates are described in detail in Supplementary Table 2. Analyses were performed using SAS v 9.4 (SAS Institute Inc, Cary, NC).

Data Availability Statement

Analysis protocols and scripts are available from the corresponding author on request. The restrictions posed by the SI and Finnish legislation do not allow open data sharing by researchers.

Standard Protocol Approvals, Registrations, and Patient Consents

According to the Finnish legislation, no ethics committee approval or patient consents were required, as de-identified register-based data was used and the participants were not contacted.

Results

Mean age of the antipsychotic initiators \((n = 19,909)\) and their matched non-initiators was 81.5 [standard deviation (SD) 6.7] years and 67% were women (Table 1). Mean time from AD diagnosis to antipsychotic initiation was 2.0 years. Initiators were more likely to have used benzodiazepines, antidepressants, and opioids. Compared with noninitiators, initiators had a higher mean number of in-hospital days within 1 year before the follow-up. Because of higher mortality among initiators, the mean duration of follow-up was shorter for initiators than noninitiators, 629 and 661 days, respectively.

During the 2-year follow-up, the mean number of accumulated hospital days was 52.5 [SD 97.7; median 15; interquartile range (IQR) 1–57] for initiators and 34.7 [SD 72.4; median 7; IQR 0–36] for non-initiators. Higher proportion of noninitiators had no hospitalizations (34.1%) during the follow-up compared with initiators (23.8%). After adjusting, initiators had 1.53 times [95% confidence interval (CI) 1.47–1.59] more hospital days than noninitiators (Table 2). Increased accumulation rate was observed for both general (adjusted IRR 1.56; 95% CI 1.49–1.63) and specialized healthcare (1.37; 1.29–1.46). All IRRs and 95% CIs were further away from 1 in the sensitivity analyses than in the main analyses (Figure 2).

Dementia was the most common reason for hospital days (Table 2). In the main analysis with ITT approach and 2-year follow-up, initiators were more likely to have a higher number of accumulated hospital days with primary diagnosis codes of dementia, mental and behavioral disorders, factors influencing health status, diseases of the respiratory, genitourinary and circulatory system, certain infectious and parasitic diseases, and symptoms not elsewhere classified, than noninitiators. The most common diagnostic code in the factors influencing health status was caregivers’ care breaks, accounting for nearly 70% of hospital days in this category for initiators and noninitiators. The most common symptoms not elsewhere classified were malaise and fatigue (36.9% and 29.3% of hospital days among initiators and noninitiators, respectively). In both sensitivity analyzes, these IRRs and 95% CIs remained the same or were further away from 1 than in the main analyses (Figure 2). In the as-treated analysis, initiators had accumulated more days because of injuries and poisonings; diseases of the digestive system; endocrine, nutritional and metabolic diseases; and diseases of the blood and blood-forming organs. Initiators had a lower number of accumulated hospital days because...
of the musculoskeletal system and connective tissue in the main analysis but not in the as-treated analysis.

The most frequently initiated antipsychotics were risperidone (62.4% of initiators) and quetiapine (29.7%) (Table 1). Quetiapine initiators were more likely to be male and use benzodiazepines, antidepressants, and opioids compared with risperidone initiators. Risperidone initiators had a longer time since AD diagnosis until initiation of use and a slightly shorter follow-up of the mean number of accumulated hospital days was 53.0 (SD 100.1; median 15; IQR 1–57) for risperidone and 50.5 (SD 92.2; median 16; IQR 1–56) for quetiapine initiators.

Table 2: Total Number of Hospital Days for Antipsychotic Initiators and Noninitiators (as a Reference)

<table>
<thead>
<tr>
<th>Total length of follow-up, person-y</th>
<th>Initiators (n = 19,909)</th>
<th>Noninitiators (n = 36,021)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospital d</td>
<td>3050</td>
<td>1918</td>
<td>.001</td>
</tr>
<tr>
<td>Days in general healthcare</td>
<td>2659</td>
<td>1640</td>
<td>.001</td>
</tr>
<tr>
<td>Days in specialized healthcare</td>
<td>414</td>
<td>297</td>
<td>.001</td>
</tr>
<tr>
<td>Days according to primary diagnosis by ICD-10 main disease groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia (F00, F03, G30)</td>
<td>1648</td>
<td>753</td>
<td>.001</td>
</tr>
<tr>
<td>Circulatory system (I)</td>
<td>291</td>
<td>282</td>
<td>.001</td>
</tr>
<tr>
<td>Respiratory system (J)</td>
<td>218</td>
<td>148</td>
<td>.001</td>
</tr>
<tr>
<td>Genitourinary system (N)</td>
<td>116</td>
<td>85</td>
<td>.001</td>
</tr>
<tr>
<td>Symptoms not elsewhere classified (R)</td>
<td>88</td>
<td>70</td>
<td>.001</td>
</tr>
<tr>
<td>Factors influencing health status (Z)</td>
<td>87</td>
<td>47</td>
<td>.001</td>
</tr>
<tr>
<td>Mental and behavioral (F)</td>
<td>75</td>
<td>34</td>
<td>.001</td>
</tr>
<tr>
<td>Infectious and parasitic (A, B)</td>
<td>66</td>
<td>49</td>
<td>.001</td>
</tr>
<tr>
<td>Nervous system (G)</td>
<td>55</td>
<td>42</td>
<td>.001</td>
</tr>
<tr>
<td>Malignant neoplasms (C)</td>
<td>44</td>
<td>48</td>
<td>.001</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue (M)</td>
<td>38</td>
<td>53</td>
<td>.001</td>
</tr>
<tr>
<td>Endocrine, nutritional, metabolic (E)</td>
<td>24</td>
<td>26</td>
<td>.001</td>
</tr>
<tr>
<td>Blood and blood-forming organs (D)</td>
<td>20</td>
<td>18</td>
<td>.001</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue (L)</td>
<td>13</td>
<td>8</td>
<td>.001</td>
</tr>
<tr>
<td>Eye, ear, nose, mouth (H)</td>
<td>9</td>
<td>7</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, time since diagnosis of AD, log(person-time), use of benzodiazepines, antidepressants, opioids, number of other than psychotropic drugs at start of follow-up, prior stroke, hip fracture, cardiovascular disease, asthma/COPD and diabetes; number of in-hospital days within one year prior to the start of follow-up.

#Excluding dementia (F03).
Fig. 2. Differences in adjusted IRRs with 95% confidence intervals between main and sensitivity analyses for accumulation of hospital days: (A) among antipsychotic initiators compared with matched noninitiators and (B) among quetiapine initiators compared with risperidone initiators.

Table 3
Total Number of Hospital Days for Risperidone (as a Reference) and Quetiapine Initiators

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risperidone Initiators</th>
<th>Quetiapine Initiators</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hospital days</td>
<td>n = 12,425</td>
<td>n = 5910</td>
</tr>
<tr>
<td>Total length of follow-up, person-y</td>
<td>21,321</td>
<td>10,322</td>
</tr>
<tr>
<td>Unadjusted IRR (95% CI)</td>
<td>0.94 (0.89—1.00)</td>
<td>0.92 (0.87—0.98)</td>
</tr>
<tr>
<td>Adjusted IRR (95% CI)</td>
<td>0.90 (0.84–0.97)</td>
<td>0.89 (0.83–0.95)</td>
</tr>
</tbody>
</table>

Days according to primary diagnosis by ICD-10 main disease groups

- Dementia (F00, F03, G30)
  - Unadjusted: 0.84 (0.76–0.93)
  - Adjusted: 0.82 (0.74–0.92)

- Circulatory system (I)
  - Unadjusted: 0.89 (0.76–1.05)
  - Adjusted: 0.96 (0.82–1.13)

- Respiratory system (J)
  - Unadjusted: 0.95 (0.80–1.13)
  - Adjusted: 0.96 (0.81–1.13)

- Injuries and poisoning (S, T)
  - Unadjusted: 1.16 (0.97–1.39)
  - Adjusted: 1.20 (1.11–1.27)

- Genitourinary (N)
  - Unadjusted: 0.84 (0.71–0.99)
  - Adjusted: 0.77 (0.66–0.91)

- Symptoms not elsewhere classified (R)
  - Unadjusted: 0.83 (0.71–0.98)
  - Adjusted: 0.77 (0.66–0.91)

- Factors influencing health status (Z)
  - Unadjusted: 1.84 (1.33–2.54)
  - Adjusted: 1.69 (1.22–2.33)

- Mental and behavioral (F)
  - Unadjusted: 1.67 (1.19–2.34)
  - Adjusted: 1.79 (1.25–2.58)

- Infectious and parasitic (A, B)
  - Unadjusted: 1.05 (0.83–1.33)
  - Adjusted: 1.00 (0.78–1.28)

- Nervous system (G)
  - Unadjusted: 2.10 (1.49–2.97)
  - Adjusted: 1.97 (1.39–2.80)

- Digestive system (K)
  - Unadjusted: 1.08 (0.70–1.65)
  - Adjusted: 1.22 (0.74–2.01)

- Malignant neoplasms (C)
  - Unadjusted: 1.32 (0.96–1.83)
  - Adjusted: 1.39 (1.00–1.93)

- Musculoskeletal, connective tissue (M)
  - Unadjusted: 1.30 (1.03–1.63)
  - Adjusted: 1.35 (1.09–1.70)

- Endocrine, nutritional, metabolic (E)
  - Unadjusted: 0.70 (0.48–1.03)
  - Adjusted: 0.61 (0.42–0.89)

- Blood and blood-forming organs (D)
  - Unadjusted: 1.18 (0.79–1.79)
  - Adjusted: 1.34 (0.87–2.05)

- Skin and subcutaneous tissue (L)
  - Unadjusted: 0.65 (0.33–1.25)
  - Adjusted: 0.68 (0.34–1.38)

- Eye, adnexa, ear, mastoid (H)
  - Unadjusted: 1.30 (1.03–1.63)
  - Adjusted: 1.35 (1.09–1.70)

- Nervous system (G)
  - Unadjusted: 1.20 (1.11–1.27)
  - Adjusted: 1.17 (1.08–1.27)

**Note:**
- *Adjusted for age, sex, time since diagnosis of AD, log(person-time), use of benzodiazepines, antidepressants, opioids, number of other than psychotropic drugs at start of follow-up; prior stroke, hip fracture, cardiovascular disease, asthma/COPD and diabetes; number of in-hospital days within 1 year prior to the start of follow-up.
- †Excluding dementia in AD (F00) and unspecified dementia (F03).
quetiapine initiators. Quetiapine initiators had a lower number of accumulated hospital days in general healthcare but a higher number of hospital days in specialized healthcare than risperidone initiators (Table 3). In the sensitivity analysis with 180 days of follow-up, these results remained similar (Figure 2), but in the as-treated analysis, quetiapine initiators no longer had a higher number of accumulated days in specialized healthcare than risperidone initiators.

In the main analysis with ITT approach and 2-year follow-up, quetiapine initiators had a higher number of accumulated hospital days because of mental and behavioral disorders, diseases of the nervous system, factors influencing health status, and injuries and poisonings compared with risperidone initiators (Table 3, Supplementary Figure 2). Quetiapine initiators had less accumulated days because of dementia, diseases of the genitourinary system, symptoms not elsewhere classified, and endocrine, nutritional, and metabolic diseases compared with risperidone initiators. The majority of these results remained significant in both sensitivity analyses, except differences in accumulation of hospital days because of mental and behavioral disorders, injuries and poisoning, and endocrine, nutritional and metabolic diseases were not statistically significant in the as-treated analyses (Supplementary Figure 2). In as-treated sensitivity analysis, quetiapine initiators had a lower number of hospital days because of infectious and parasitic diseases and diseases of the respiratory system.

Discussion

Antipsychotic initiation was associated with a higher number of accumulated hospital days among community dwellers with AD. This result is in line with previous studies reporting higher risk of unplanned hospitalization among older antipsychotic users.10,11 and may reflect the occurrence of adverse effects and higher risk of serious adverse events such as pneumonia, stroke, myocardial infarction, acute kidney injury, and hip fracture associated with antipsychotic use.1,7-23,24 Accordingly, in this study antipsychotic initiators had a higher number of hospital days with primary diagnosis categories such as diseases of respiratory, circulatory, and genitourinary system, as well as infectious and parasitic diseases. In addition, they accumulated more hospital days because of malaise and fatigue, which may be related to adverse effects.

Antipsychotic initiators were more likely to accumulate hospital days with diagnoses of dementia and mental and behavioral disorders than noninitiators. Admission data, classified with ICD-10 codes, did not contain more elaborate information on the reasons behind the hospitalization because of dementia. It may reflect, for example, BPDS, optimization of treatment, or rehabilitation. Antipsychotic initiators also accumulated more hospital days because of factors influencing health status, which was mainly driven by the caregivers’ break from caregiving. The indication for antipsychotic use, severity of BPDS, and subsequent caregiver burden likely explains these findings. These results may also reflect difficulties in the treatment of most severe BPDS and the modest effectiveness of antipsychotics5,25-28 or their potential adverse effects on cognitive function.29 The register-based data did not include information on indication for antipsychotic use or severity of AD or BPDS. Therefore, noninitiators were matched based on time since AD diagnosis and analyses were adjusted for use of other psychotropics as proxies of BPDS. Number of prior hospital days was also adjusted in the analyses, as antipsychotic initiators had a higher mean number of hospital days during the year prior to initiation, which may reflect the differences in severity of symptoms and the underlying health problems triggering BPDSs between initiators and non-initiators.

Quetiapine initiators accumulated less days because of dementia, but more hospital days because of mental and behavioral disorders and diseases of the nervous system. This may reflect the differences in type and severity of symptoms for which risperidone and quetiapine were initiated and the effectiveness of these antipsychotics. Quetiapine has no evidence on efficacy in the treatment of BPDS.29,30 Risperidone is the only antipsychotic in Finland with approved indication for the short-term treatment of severe aggression among persons with moderate to severe AD. Quetiapine is frequently used with low doses in the treatment of insomnia.31 Thus, it is likely that risperidone was more frequently used to treat more severe BPDS, and the indication may have increased the need for hospital care.

Quetiapine initiators accumulated more hospital days because of injuries and poisonings, but they had less hospital days because of diseases of the genitourinary system, symptoms not elsewhere classified, and endocrine, nutritional, and metabolic diseases. Risperidone and quetiapine have different receptor-binding affinities and consequently different adverse effect profiles.25 D2 receptor blockade can lead to extrapyramidal symptoms (EPS).25 Of atypical antipsychotics, risperidone is associated with the highest risks of EPS whereas quetiapine has one of the lowest risks.2/. Sedation is mediated via H1 receptor blockade and quetiapine is considered more sedative than risperidone.20,34 The risk of orthostatic hypotension correlates positively with the affinity for α1-adrenoceptors relative to dopamine D2 receptors, and both quetiapine and risperidone have a moderate risk of orthostatic hypotension.31 Sedation, orthostatic hypotension, and EPS have been suggested to contribute to the increased risks of falls and subsequent fractures associated with antipsychotic use.32,33 In this study, quetiapine was associated with a higher number of accumulated hospital days because of injuries, which could be related to differences in the risk of falls. However, previous studies on risk of falls and hip fractures associated with risperidone and quetiapine are inconclusive.34,35 In a previous MEDALZ study, there was no difference in risk of hip fracture between quetiapine and risperidone during the first 2.7 years of use.1 Further research is needed to clarify whether these differences in accumulation of hospital days are related to varying adverse effects of these 2 drugs. Previous studies have reported a higher risk of serious bacterial infections,35 including pneumonia,67 associated with risperidone compared with quetiapine. In the as-treated analyses, quetiapine initiators had a lower number of accumulated hospital days because of diseases of the respiratory system, and certain infectious and parasitic diseases.

Strengths and Limitations

A strength of this study was the nationwide register-based cohort of all community dwellers with clinically verified diagnoses of AD. The Finnish Care Register for Healthcare covers more than 95% of discharges.28 Although all-cause hospitalizations have been implied to proxy overall drug safety,12 these results stress the importance of investigating the underlying diagnoses. Thus, ability to analyze the hospital day accumulation according to main diagnosis categories is a strength of this study.

A limitation of the study is lack of information on whether antipsychotics were used, discontinued, or initiated during hospitalizations. The ITT approach was applied because accumulation of hospital days was the main outcome, but at the same time the exposure status is unknown during these periods. In sensitivity analyses, the follow-up was shortened from 2 years to 180 days, and with as-treated approach follow-up was censored if initiators discontinued or noninitiators initiated antipsychotic use. In these sensitivity analyses, all IRRs and 95% CIs for the differences in accumulation of hospital days between initiators and noninitiators were further away from 1 than in the main analyses. During a shorter follow-up time fewer changes in exposure status are likely to happen and, therefore, there is less misclassification of exposure time. The BPDS for which antipsychotics were initiated might be more severe at the time of initiation and the risk of adverse effects and events may be higher shortly after initiation of antipsychotic use. Both factors could increase the accumulation of
hospital days for antipsychotic initiators in shorter follow-up. A limitation of the register-based data was lack of information on indication of drug use or severity of BPDS or AD. The users and nonusers were matched by time since AD diagnosis and analyses were adjusted for use of other psychotropics, but residual confounding by indication may exist. The study was restricted to community dwellers, and the results are, therefore, not representative of institutionalized persons.

Conclusions and Implications

Antipsychotic initiators accumulated more hospital days than noninitiators, especially within the first 6 months. Part of the hospitalizations may be related to adverse events or events. The results may also reflect difficulties in treating the most severe BPDSs and the underlying health problems triggering BPDSs, such as infections. These findings indicate the necessity for careful and regular monitoring of antipsychotic use to assess the response and decrease the risk of adverse events.

References

Appendix

**Supplementary Fig. 1.** Differences in adjusted IRRs with 95% CIs between main and sensitivity analyses for accumulation of hospital days according to ICD-10 chapters among antipsychotic initiators compared with noninitiators. Adjusted for age, sex, time since diagnosis of AD, log(person-time), use of benzodiazepines, antidepressants, opioids, number of other than psychotropic drugs at start of follow-up; prior stroke, hip fracture, cardiovascular disease, asthma/COPD and diabetes; number of in-hospital days within 1 year prior to the start of follow-up. Main analysis was ITT approach with 2-year follow-up; first sensitivity analysis was ITT approach with 180-day follow-up; second sensitivity analysis was as-treated approach with maximum follow-up of 2 years.

**Supplementary Fig. 2.** Differences in adjusted incidence rate ratios (IRRs with 95% CIs) between main and sensitivity analyses for accumulation of hospital days according to ICD-10 main chapters among quetiapine compared with risperidone initiators. Adjusted for age, sex, time since diagnosis of AD, log(person-time), use of benzodiazepines, antidepressants, opioids, number of other than psychotropic drugs at start of follow-up; prior stroke, hip fracture, cardiovascular disease, asthma/COPD and diabetes; number of in-hospital days. Main analysis was ITT approach with 2-year follow-up; first sensitivity analysis was ITT approach with 180-day follow-up; second sensitivity analysis was as-treated approach with maximum follow-up of 2 years. The y axis was cut to 4. The actual upper CI is 5.96 for skin and subcutaneous tissue in the ITT analysis with 180-day follow-up.
**Supplementary Table 1**  
Hospital Days Were Classified Based on the Primary Discharge Diagnosis According to the Chapters of the ICD-10 Classification

<table>
<thead>
<tr>
<th>Chapters of the ICD-10 Classification</th>
<th>Name of the Chapter</th>
<th>Modified Categorizations Used in the Analyses</th>
<th>Shorter Name Used in Tables 2 and 3 and Supplementary Figures 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A00-B99</td>
<td>Certain infectious and parasitic diseases</td>
<td>Malignant neoplasms (C*)</td>
<td>Infectious and parasitic</td>
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<tr>
<td>C00-D48</td>
<td>Neoplasms</td>
<td>Other neoplasms and diseases of the blood and blood-forming organs and certain disorders involving immune mechanism</td>
<td>Blood and blood-forming organs</td>
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<tr>
<td>D50-D89</td>
<td>Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism</td>
<td></td>
<td></td>
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<tr>
<td>E00-E90</td>
<td>Endocrine, nutritional and metabolic diseases</td>
<td>Excluding Dementia in AD (F00) and Unspecified dementia (F03)</td>
<td>Endocrine, nutritional, metabolic</td>
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<tr>
<td>F</td>
<td>Mental and behavioral disorders</td>
<td>Excluding AD (G30)</td>
<td>Mental and behavioral</td>
</tr>
<tr>
<td>G</td>
<td>Diseases of the nervous system</td>
<td>Dementia including F00, P03, G30</td>
<td>Nervous system</td>
</tr>
<tr>
<td>H00-H59</td>
<td>Diseases of the eye and adnexa</td>
<td>Diseases of the eye, adnexa, ear and mastoid process (H*)</td>
<td>Eye, adnexa, ear, mastoid</td>
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<tr>
<td>H60-H95</td>
<td>Diseases of the ear and mastoid process</td>
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<td></td>
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<tr>
<td>I00-I99</td>
<td>Diseases of the circulatory system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J00-J99</td>
<td>Diseases of the respiratory system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K00-K93</td>
<td>Diseases of the digestive system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L00-L99</td>
<td>Diseases of the skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M00-M99</td>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td></td>
<td></td>
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<tr>
<td>N00-N99</td>
<td>Diseases of the genitourinary system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R00-R99</td>
<td>Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S00-T98</td>
<td>Injury, poisoning and certain other consequences of external causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z00-Z99</td>
<td>Factors influencing health status and contact with health services</td>
<td></td>
<td></td>
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</tbody>
</table>
### Supplementary Table 2
Definitions for Covariates

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Classification</th>
<th>Measurement Period</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>At the index date</td>
<td>PR</td>
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<tr>
<td>Occupational socioeconomic position</td>
<td></td>
<td>Highest position recorded since 1972 until 3 years prior to the diagnosis of AD</td>
<td>SF</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td>FCR, PR, SRR</td>
</tr>
<tr>
<td>Active cancer</td>
<td></td>
<td>Within 1 y preceding the index date</td>
<td></td>
</tr>
<tr>
<td>History of schizophrenia or bipolar disorder</td>
<td>Schizophrenia, schizotypal or delusional disorders including ICD-10 codes F20-29; ICD-9 codes 295*, 297*, 298*, 3010, 3012; and ICD-8 codes 295*, 297*, 298*, 29999, 30100, 30120 or bipolar disorder including ICD-10 codes F30-31; ICD-9 codes 2962, 2963, 2964, 2967, and ICD-8 codes 29610, 29620, 29630, 29688, 29699</td>
<td>FCR</td>
<td></td>
</tr>
<tr>
<td>History of hip fracture</td>
<td>ICD-10 codes S72.0–S72.2; ICD-9 codes 820</td>
<td>FCR</td>
<td></td>
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<tr>
<td>History of stroke</td>
<td>ICD-10 codes I60–I64; ICD-9 codes 430–432, 4360, 4330A, 4331A, 4339A, 4349A, 4340A, 4341A</td>
<td>FCR</td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular disease</td>
<td>Special reimbursement classification numbers: 201 (chronic heart failure); 206, 213, 280 (coronary artery disease); 205 (arterial hypertension); 207 (cardiac arrhythmia)</td>
<td>SRR</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Special reimbursement classification number: 103</td>
<td>SRR</td>
<td></td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>Special reimbursement classification numbers: 203, 210</td>
<td>SRR</td>
<td></td>
</tr>
<tr>
<td>Number of in-hospital days</td>
<td>Special reimbursement classification numbers: 203, 210</td>
<td>FCR</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td>ATC codes</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>N06A</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>N03A</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines and related drugs</td>
<td>Benzodiazepines N05BA, N05CD and/or Z-drugs N05CF</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>N02A</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Total number of concurrent medications (other than psychotropics)</td>
<td>Sum of ATC codes (excluding N05A, N05BA, N05CD, N05CF, N06A)</td>
<td>PR</td>
<td></td>
</tr>
</tbody>
</table>

ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; FCR, Finnish Care Register for Health Care; NOMESCO, The Nordic Medico-Statistical Committee; PR, Prescription Register; SF, Statistics Finland; SII, Social Insurance Institution of Finland; SRR, Special Reimbursement Register.