Antipsychotic Use and the Risk of Hip Fracture Among Community-Dwelling Persons With Alzheimer's Disease

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ABSTRACT

Objective: To study whether antipsychotic use is associated with a risk of hip fracture among individuals with Alzheimer's disease and to compare the risk according to the duration of use and the 2 most frequently used antipsychotics.

Methods: The MEDALZ (Medication and Alzheimer's disease) cohort consisted of community-dwelling Finnish persons with clinically verified diagnoses of Alzheimer's disease, including 70,718 persons newly diagnosed according to NINCDS-ADRDA and *DSM-IV* criteria between 2005 and 2011. Antipsychotic use was modeled from prescription register data, and hip fractures (*ICD-10* S72.0–72.2) were identified from the Hospital Discharge Register. The incidence of hip fractures was compared between new users and nonusers of antipsychotics, among various time durations of antipsychotic use, and between quetiapine users and risperidone users.

Results: Antipsychotic use versus nonuse was associated with an increased risk of hip fractures (adjusted hazard ratio [HR] = 1.54; 95% CI, 1.39–1.70). The risk was increased from the first days of use and remained increased thereafter. Quetiapine was associated with a similar risk of hip fracture as risperidone for the first 2.7 years of use (adjusted HR = 0.98; 95% CI, 0.79–1.21). Compared with low-dose (≤ 0.5 mg) risperidone use, higher risperidone doses (> 0.5 mg) were associated with a higher risk of hip fracture (adjusted HR = 1.72; 95% CI, 1.32–2.24).

Conclusions: Since the risk of hip fracture was increased from the first days of use, our results confirm the need for setting a high threshold for initiating antipsychotic use among persons with Alzheimer's disease to avoid serious adverse events. If antipsychotic use is initiated, the duration of use should be limited, as the risk of hip fracture does not attenuate with long-term use.

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Hip fractures cause great suffering to individuals and place a major burden on the public health care budget. They have been associated with a decreased quality of life and an increased risk of disability, institutionalization, and mortality.[1–3] Individuals with Alzheimer's disease have a 2- to 3-fold higher risk of hip fracture compared with older people without Alzheimer's disease.[4,5] In addition, persons with Alzheimer's disease experience a higher level of mortality after hip fracture.[4]

Antipsychotic use has been previously associated with an increased risk of hip fracture among older people.[6–9] Although antipsychotics are frequently used to treat behavioral and psychological symptoms among Alzheimer's disease patients,[10–12] there are no previous studies on the risk of hip fractures associated with antipsychotic use in this vulnerable population. Furthermore, more information is needed on hip fracture risk in relation to the duration of antipsychotic use and the comparative safety of individual antipsychotics as a way of guiding treatment practices.

Our objective was to study whether antipsychotic use would be associated with an increased risk of hip fracture among community-dwelling persons with Alzheimer's disease. In addition, we determined whether the risk varied with the duration of antipsychotic use and whether there would be any differences in the hip fracture risk between the 2 most frequently used antipsychotic substances in this population, risperidone and quetiapine.

METHODS

Study Cohort

This study is based on the nationwide register-based MEDALZ (Medication and Alzheimer's disease) cohort. The MEDALZ cohort includes all 70,718 persons newly diagnosed with Alzheimer's disease between 2005 and 2011 in Finland. Individuals with Alzheimer's disease were identified from the Special Reimbursement Register maintained by the Social Insurance Institution of Finland (SII). This register contains records of persons who are entitled to higher reimbursement due to chronic diseases, such as Alzheimer's disease, diabetes, and cardiovascular diseases.[13] To be entitled to reimbursement for antidementia drugs, a patient must meet predefined criteria for Alzheimer's disease and a diagnosis statement must be submitted to the SII for approval. The SII requires that the medical statement must verify that the patient has (1) presence of symptoms consistent with Alzheimer's disease, (2) experienced a decrease in social capacity over a period of at least 3 months, (3) received a computed tomography or magnetic resonance imaging scan, (4)

Clinical Points

- More information is needed on the risk of hip fracture in relation to the duration of antipsychotic use and on the comparative safety of individual antipsychotics as treatment for behavioral and psychological symptoms.
- If antipsychotic use is deemed necessary, it is essential to weigh the risk-benefit evidence of individual antipsychotics, use the lowest effective dose, and limit the duration of use.

had possible alternative diagnoses excluded, and (5) received confirmation of the diagnosis by a registered geriatrician or neurologist. The SII reviews all medical statements and checks that the diagnosis of Alzheimer's disease is based on the NINCDS-ADRDA[14] and *DSM-IV* criteria for Alzheimer's disease. Individuals with dementia related to Parkinson's disease were excluded from this study. Data were deidentified by the SII before submission to the research group. Mean age of the cohort was 79.6 years (SD = 7.2), and 65% were female.

Antipsychotic Use Periods

All reimbursed prescription drug purchases from 1995–2012 were extracted from the Prescription Register. Drugs may be dispensed for a maximum of 3 months of treatment per purchase. The prescription register includes information on dates of dispensing, name, strength, and dosage form of the dispensed drug, the Nordic article number of the package, package size, and number of packages dispensed. In addition, the purchased amount of drug is recorded as defined daily doses, and the drugs are categorized according to Anatomic Therapeutic Chemical (ATC) classification system.[15]

Drug use periods (the start and end dates of continuous drug use) were created from prescription drug purchases with the PRE2DUP method. The logic and operation of the PRE2DUP method has been described in more detail by Tanskanen et al.[16] Briefly, the method is based on mathematical modeling of personal purchasing behavior. The method uses individual purchase histories to calculate temporal sliding averages of daily dose (in defined daily dose). It decides whether the purchased amount is enough to last to the next purchase by calculating the expected refill time according to the personal temporal daily dose. In these decisions, the method takes into account stockpiling of drugs, personal purchase regularity, and possible periods of hospital and nursing home care when drugs are provided by these institutions and not recorded in the register. The method constructs drug use periods for each person and for each ATC code. For the analysis of antipsychotic use compared with no use, drug use periods of individual antipsychotics were combined to retrieve use of "any antipsychotics." During the periods of "any antipsychotic" use, subjects were allowed to switch between different antipsychotics and use more than 1 antipsychotic concomitantly. Prochlorperazine (N05AB04) and lithium (N05AN01) were excluded from the definition of antipsychotics (N05A).

Outcome

Hip fractures were identified from the Hospital Discharge Register based on *ICD-10* codes: S72.0 (fracture of neck of femur), S72.1 (pertrochanteric fracture), and S72.2 (subtrochanteric fracture). Persons who had experienced a hip fracture before the beginning of the follow-up were excluded. Thus, the main outcome was incident hip fracture.

Confounders

We adjusted for age, sex, comorbidities, and use of drugs known to be associated with a risk of hip fracture[17–20] and that could affect antipsychotic prescribing. Data on diabetes, rheumatoid arthritis, epilepsy, glaucoma, and cardiovascular diseases including chronic heart failure, chronic arterial hypertension, coronary artery disease, and chronic arrhythmias were obtained from the Special Reimbursement Register.[13] Data on a history of stroke preceding the start of follow-up were extracted from the Hospital Discharge Register using *ICD-10* codes I60–I64. A history of drug use to treat osteoporosis was used as a proxy for osteoporosis. The use of drugs affecting bone structure and mineralization (M05B) was extracted from the prescription register data. In addition, we took into account the use of opioids (N02A) and consumption of other psychotropic drugs, including benzodiazepines and related drugs (N05BA, N05CF, N05CD), antidepressants (N06A), and antidepressants in combination with psycholeptics (N06C).

We excluded persons with a history of schizophrenia, schizotypal or delusional disorders, or bipolar disorder, as we wanted to study the risks of antipsychotic use in the treatment of behavioral and psychological symptoms. Data on history of schizophrenia and schizotypal and delusional disorders (*ICD-10* codes F20–F29; *ICD-9* codes 295, 297, 298, 301.0, and 301.2; *ICD-8* codes 295, 297, 298, 299.99, 301.00, and 301.20) and bipolar disorder (*ICD-10* codes F30–F31; *ICD-9* codes 296.2, 296.3, 296.4, and 296.7; *ICD-8* codes 296.10, 296.20, 296.30, 296.88, and 296.99) were collected from the Hospital Discharge Register (data available since 1972). Only diagnoses from hospitalizations occurring at least 5 years before the diagnosis of Alzheimer's disease were considered.

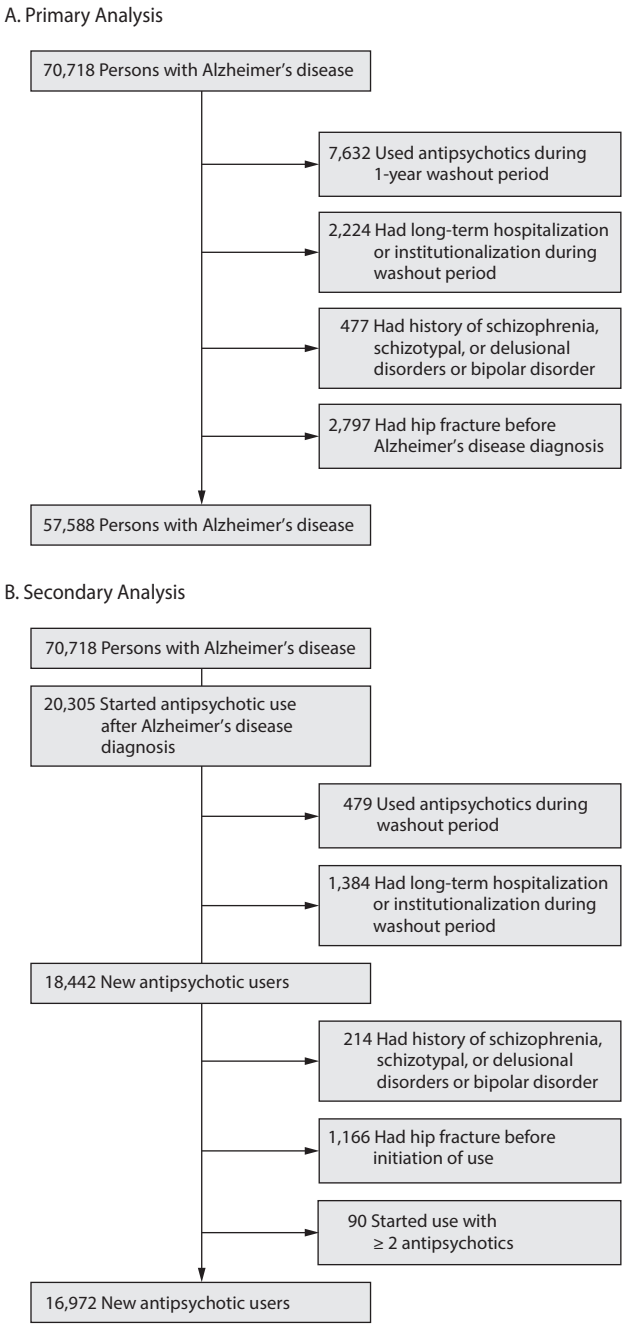
Ethical Aspects

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

Statistical Analysis

In the primary analyses, the incidence of hip fracture during antipsychotic use was compared with incidence during no use. The follow-up started at the date of Alzheimer's disease diagnosis. A 1-year washout period preceding the Alzheimer's disease diagnosis was applied, as we wanted to focus on new users of antipsychotics and avoid prevalent user bias. All persons (n = 7,632)

Figure 1. Formation of Study Sample



who used antipsychotics during the washout period were excluded. As the prescription register does not cover drugs used in nursing homes and hospitals, we excluded persons who were hospitalized or institutionalized for ≥ 6 months during the washout period, had an ongoing hospital stay of ≥ 90 days at the last date of the washout period, or were hospitalized during the entire follow-up. The formation of the study sample (n = 57,588) and reasons for exclusions are summarized in Figure 1A. From the start of follow-up, the antipsychotic use status was treated as a time-dependent covariate. The follow-up was censored at the date of first hip fracture, death, or start of long-term institutionalization or hospitalization; discontinuation of antipsychotic use; or end of the study period (December 31, 2012), whichever occurred first. The follow-up was censored at the first discontinuation of antipsychotic use, as those who survive the first treatment period and subsequently restart use are likely to be different from those that discontinue use and never start treatment with antipsychotics again or are censored due to institutionalization or death. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards model. The analyses were adjusted for time-dependent (use of other psychotropic drugs and opioids) and baseline (age, sex, comorbidities) variables. To analyze whether the hip fracture risk varied with the duration of antipsychotic use, we classified the duration of use time dependently into 4 categories: ie, ≤ 30 days, 31–180 days, 181–365 days, and over 365 days of use.

In the secondary analyses, hip fracture risk was compared between the most frequently used antipsychotic drugs. All new antipsychotic users were identified after the date of Alzheimer's disease diagnosis. The washout period was 1 year preceding the initiation of antipsychotic use. The follow-up for hip fractures started from the date of initiation of first antipsychotic use, and individuals with hip fractures before that date were excluded. The formation of the study sample (n = 16,972) and reasons for exclusions are summarized in Figure 1B. In addition, individuals who initiated antipsychotic use with concomitant use of ≥ 2 antipsychotics were excluded from this analysis to compare the risk of individual antipsychotic drugs. Similarly, the follow-up was censored if the user switched to a different antipsychotic drug, started using ≥ 2 antipsychotics concomitantly, or discontinued use. Also, the follow-up was censored at the date of first hip fracture, the start of long-term institutionalization or hospitalization, death, after 1,500 days of antipsychotic use, or the end of the study period (December 31, 2012), whichever occurred first. The follow-up time was restricted to the first 1,500 days of use to avoid sparsity of the data, and analyses were restricted to the 2 most frequently used antipsychotics, risperidone (n = 10,630) and quetiapine (n = 4,990), because of the low number of users of other antipsychotic drugs (see eAppendix 1). In the Cox proportional hazards model, quetiapine use was compared with risperidone use. The sample log cumulative hazard functions were used to evaluate the proportional hazards assumption. According to these, the risk of hip fracture was equal among users of risperidone and quetiapine during the first 1,000 days, but thereafter remained higher for risperidone than for quetiapine. Thus, a cutoff point of 1,000 days was applied along with the programming statement method. In addition, the effect of dose on hip fracture risk was analyzed. Dose represents the average dose from the entire antipsychotic use period. Quetiapine doses were categorized into ≤ 50 mg and > 50 mg, and risperidone doses were categorized into ≤ 0.5 mg (reference category) and > 0.5 mg. All analyses were performed with SAS (Version 9.3; SAS Institute, Cary, North Carolina).

Table 1. Characteristics of Persons With Alzheimer's Disease According to Antipsychotic Use

Characteristic	Antipsychotic Use (n = 15,942)		No Use During Follow-Up (n = 41,646)		Odds Ratio		Quetiapine (n = 4,990)		Risperidone (n = 10,630)		Odds Ratio	
	n	%	n	%	Estimate	95% CI	n	%	n	%	Estimate	95% CI
Age, y												
< 75	3,884	24.4	8,461	20.3	1.00		919	18.4	1,745	16.4	1.00	
75–84	8,988	56.4	23,382	56.1	0.84	0.80–0.88	2,652	53.2	5,656	53.2	0.89	0.81–0.98
≥ 85	3,070	19.3	9,803	23.5	0.68	0.65–0.72	1,419	28.4	3,229	30.4	0.83	0.75–0.92
Female sex	10,233	64.2	26,541	63.7	1.02	0.98–1.06	3,106	62.2	6,993	65.8	0.86	0.80–0.92
History of stroke	1,308	8.2	3,877	9.3	0.87	0.82–0.93	524	10.5	1,055	9.9	1.07	0.95–1.19
Osteoporosis	1,963	12.3	5,809	14.0	0.87	0.82–0.92	759	15.2	1,513	14.2	1.08	0.98–1.19
Diabetes	1,783	11.2	5,760	13.8	0.78	0.74–0.83	618	12.4	1,320	12.4	1.00	0.90–1.10
Cardiovascular disease	7,974	50.0	21,318	51.2	0.95	0.92–0.99	2,604	52.2	5,396	50.8	1.06	0.99–1.13
Glaucoma	1,360	8.5	3,841	9.2	0.92	0.86–0.98	452	9.1	989	9.3	0.97	0.86–1.09
Rheumatoid arthritis	636	4.0	1,872	4.5	0.88	0.81–0.97	194	3.9	439	4.1	0.94	0.79–1.12
Epilepsy	224	1.4	878	2.1	0.66	0.57–0.77	79	1.6	210	2.0	0.80	0.62–1.04
Use of benzodiazepines	3,346	21.0	7,579	18.2	1.19	1.14–1.25	1,589	31.8	3,171	29.8	1.10	1.02–1.18
Use of antidepressants	2,963	18.6	7,363	17.7	1.06	1.01–1.11	1,518	30.4	2,983	28.1	1.12	1.04–1.21
Use of opioids	457	2.9	1,550	3.7	0.76	0.69–0.85	313	6.3	563	5.3	1.20	1.04–1.38

Table 2. Hip Fracture Rates and Hazard Ratios According to Antipsychotic Use and Duration of Use

Variable	Person-Years of Use	No. of Hip Fractures	Incidence Rate Per 100 Person-Years		Crude Hazard Ratio		Adjusted Hazard Ratio[a]	
			Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
No use	143,671	2,493	1.74	1.73–1.74	1.00		1.00	
Antipsychotic use	16,587	478	2.88	2.86–2.91	1.61	1.45–1.78	1.54	1.39–1.70
Duration of antipsychotic use, d[b]								
1–30	1,264	39	3.09	2.99–3.18	1.84	1.34–2.53	1.76	1.28–2.41
31–180	4,603	124	2.69	2.64–2.74	1.57	1.31–1.89	1.52	1.26–1.82
181–365	3,619	92	2.54	2.49–2.59	1.45	1.18–1.79	1.40	1.14–1.73
> 365	7,101	223	3.14	3.10–3.18	1.68	1.46–1.94	1.60	1.39–1.85

[a]Analyses were adjusted for sex, age, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease, and epilepsy. Use of other psychotropics and opioids were treated as time-dependent covariates.
[b]"No use" is the reference group in the duration analysis.

RESULTS

The median follow-up time was 2.4 years (interquartile range [IQR], 1.4–3.9). During the follow-up period, a substantial proportion, ie, 27.7% (15,942/57,588), of individuals with Alzheimer's disease started using antipsychotics. The antipsychotic initiators were more likely to be younger and users of benzodiazepines and antidepressants at the date of Alzheimer's disease diagnosis compared with those who did not use antipsychotics during the follow-up period (Table 1). On the other hand, antipsychotic users were less likely to have history of stroke, osteoporosis, diabetes, cardiovascular disease, glaucoma, rheumatoid arthritis, and epilepsy and less likely to be users of opioids at the time of Alzheimer's disease diagnosis.

During the periods of antipsychotic use, the rate of hip fractures was 2.88 (95% CI, 2.86–2.91) per 100 person-years compared with 1.74 (95% CI, 1.73–1.74) hip fractures occurring per 100 person-years of nonuse (Table 2). The absolute difference in incidence rates was 1.15 hip fractures per 100 person-years (95% CI, 1.12–1.17). Antipsychotic use was associated with a 1.61 times elevated risk of experiencing a hip fracture in individuals with Alzheimer's disease. Adjusting for age, sex, comorbidities, and use of other psychotropic drugs and opioids did not attenuate the association to any extent. The association between antipsychotic use and hip fracture was similar in all age groups and between the sexes (for interaction with age and sex, $P = .25$ and $P = .10$, respectively). The risk of hip fracture was elevated from the first days of use and remained elevated with long-term use (Table 2).

Drug-drug comparison included 10,630 new risperidone users and 4,990 quetiapine users. Median follow-up time was 189 days (IQR, 72–474). Quetiapine users were more likely to be younger and male and more likely to use benzodiazepines, antidepressants, and opioids compared with risperidone users (Table 1). During 5,344 person-years of quetiapine use, 143 incident hip fractures occurred in comparison with 272 hip fractures during 8,933 person-years of risperidone use (adjusted HR = 0.89; 95% CI, 0.72–1.09) (Table 3). There was no difference in hip fracture risk between quetiapine and risperidone during the first 2.7 years of use. However, from 2.7 to 4.1 years, the hip fracture risk was lower among quetiapine users compared with risperidone users.

The median dose of risperidone was 0.7 mg (IQR, 0.5–0.9). Quetiapine was used at a median dose of 31 mg (IQR, 21–51). In comparison with low-dose (≤ 0.5 mg) risperidone use, higher risperidone doses (> 0.5 mg) were associated with a higher risk of hip fracture (HR = 1.72; 95% CI, 1.32–2.24; adjusted for sex, age, comorbidities, and use of

Table 3. Comparison of the Hip Fracture Risk Between Quetiapine and Risperidone Users

Variable	No. of Users	Person-Years of Use	No. of Hip Fractures	Incidence Rate per 100 Person-Years		Crude Hazard Ratio		Adjusted Hazard Ratio[a]	
				Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Risperidone	10,630	8,933	272	3.04	3.01–3.08	1.00		1.00	
Quetiapine	4,990	5,344	143	2.68	2.63–2.72	0.87	0.71–1.07	0.89	0.72–1.09
≤ 1,000 d									
Risperidone	10,630	8,453	247	2.92	2.89–2.96	1.00		1.00	
Quetiapine	4,990	4,882	137	2.81	2.76–2.85	0.96	0.78–1.18	0.98	0.79–1.21
1,001–1,500 d									
Risperidone	642	481	25	5.20	5.00–5.41	1.00		1.00	
Quetiapine	540	462	6	1.30	1.19–1.40	0.25	0.10–0.61	0.24	0.10–0.59
Dose analyses									
Risperidone ≤ 0.5 mg	4,250	3,397	79	2.33	2.27–2.38	1.00		1.00	
Risperidone > 0.5 mg	6,380	5,536	193	3.49	3.44–3.54	1.50	1.16–1.95	1.72	1.32–2.24
Quetiapine ≤ 50 mg	3,724	3,631	101	2.78	2.73–2.84	1.19	0.87–1.60	1.28	0.95–1.72
Quetiapine > 50 mg	1,266	1,713	42	2.45	2.38–2.53	1.04	0.71–1.51	1.22	0.84–1.78

[a]Analyses were adjusted for sex, age, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease, epilepsy, use of other psychotropics, and opioids at the time of antipsychotic initiation.

other psychotropic drugs and opioids). The administration of both low and high doses of quetiapine use (ie, ≤ 50 mg and > 50 mg) was associated with a similar hip fracture risk as low-dose risperidone use (adjusted HR = 1.28 [95% CI, 0.95–1.72] and adjusted HR = 1.22 [95% CI, 0.84–1.78], respectively).

DISCUSSION

Antipsychotic use was associated with an increased risk of hip fracture among community-dwelling individuals with Alzheimer's disease. The risk of hip fracture was increased from the first days of use and remained elevated with long-term use. Current care guidelines recommend time-limited use of antipsychotics in the treatment of the most severe behavioral and psychological symptoms, including aggression, agitation, and psychosis.[21,22] As the risk of hip fracture was increased soon after treatment initiation and was evident with short-term use, these results highlight the need to have a high threshold before prescribing antipsychotics to individuals with Alzheimer's disease. If antipsychotic use is deemed necessary, the duration of use should be limited, as the risk of hip fracture did not attenuate with long-term use.

In contrast to our results, a case-control study by Jalbert et al[23] did not find increased hip fracture risk among nursing home residents with dementia treated with antipsychotics for less than 6 months but reported an increased risk with a longer duration of use. The fact that they did not detect risk during short-term use may be due to the small number of short-term users in that study and a prevalence bias causing underdetection of hip fractures occurring soon after the initiation of antipsychotic use. We limited analyses to incident users to avoid this bias. Two other case-control studies[24,25] including persons aged 18 years or older did detect an increased hip fracture risk shortly after initiation of antipsychotic use and higher or similar risk in long-term use. Antipsychotics are known to cause sedation, orthostatic hypotension, and extrapyramidal side effects,[26] which could lead to increased risk of falls and fractures. Sedation refers to objectively measured decreased psychomotor functioning in addition to subjective feelings of drowsiness.[27,28] The sedative effects of drugs may result in impaired physical function, but the mechanisms behind this phenomenon are not fully understood. It is likely that mechanisms leading to mobility limitation are multidimensional; they may be caused by slowing of neuromuscular processing in the central nervous system, muscle-relaxant effects, and reduced muscle functioning.[29–32] Orthostatic hypotension and low blood pressure reduce cerebral perfusion leading to dizziness and an increased risk of falling.[33] Extrapyramidal symptoms have been associated with postural instability, which in turn may predispose to falls.[34] In addition, it has been postulated that with long-term use, certain antipsychotics (first-generation antipsychotics, risperidone) could decrease bone mineral density via hyperprolactinemia, which increases the risk of fracture should the individual experience a fall.[25,26,35]

Risperidone and quetiapine were the most commonly used antipsychotics in our study cohort. Risperidone is the only antipsychotic drug officially approved for treatment of behavioral and psychological symptoms,[21,36] which explains its extensive use. Finnish guidelines for the care of cognitive disorders recommend that atypical antipsychotics are the preferred choice.[21] The popularity of quetiapine may be related to its off-label use, for example, in the treatment of insomnia.[37] Although there are reports describing the modest efficacy of risperidone, olanzapine, and aripiprazole in the treatment of aggression and psychosis, there is a lack of evidence on efficacy of quetiapine use in the treatment of Alzheimer's disease.[38,39]

Based on our results, the risk of hip fracture is similar in risperidone and quetiapine use at least for the first 2.7 years of use. From 2.7 to 4.1 years of use, the hip fracture risk seemed to be lower among quetiapine users compared with the risperidone users. However, this result should be interpreted with caution because of the highly selected sample of users surviving and remaining as users for this long time. Thus, we cannot conclude that quetiapine would be safer for long-term use. It should be emphasized that the guidelines[21,22] recommend time-limited use of antipsychotics in the treatment of the most severe behavioral and psychological

symptoms, with regular reviews conducted every 3 to 6 months. Two other cohort studies with a new-user design that obtained results similar to ours found no differences in hip fracture rates between individual antipsychotic drugs among old nursing home residents during 180 days[7] and 1–293 days (average 93)[8] of follow-up. Thus, none of the individual antipsychotic drugs can be considered safer than the others with respect to the risk of hip fracture.

Our finding that risperidone use with a dose >0.5 mg was associated with a higher risk of hip fracture supports the recommendation that if antipsychotics are initiated, then it is important that the lowest effective dose should be used in Alzheimer's disease patients.[21,22] Quetiapine was mainly administered in low doses, as 3 of every 4 users consumed this drug at doses ≤50 mg, which may explain why we did not find a dose-response in hip fracture risk with quetiapine use.

The management and treatment of behavioral and psychological symptoms is a complex issue among individuals with Alzheimer's disease. Nonpharmacologic options are recommended as the first-line treatment.[21,22,36] Other pharmacologic options as alternatives to antipsychotics are limited and have shown very limited evidence for efficacy and safety.[36] For these reasons, antipsychotic use should be limited to relieving the most severe symptoms that pose a danger to the patient or others or relieving unnecessary suffering such as hallucinations. Antipsychotics should be used only for the symptoms for which there is demonstrated efficacy, with the benefits always weighed against the harms and termination of treatment or at least reduction of the dose as soon as the psychotic symptoms have alleviated.

Strengths and Limitations

The important strength of this study is the large nationwide cohort of community-dwelling persons with clinically and imaging verified diagnoses of Alzheimer's disease. In addition, we applied a new-user design to capture early events occurring soon after treatment initiation. The Hospital Discharge Register has been shown to be a valid data source, capturing nearly all hip fractures (98%).[40] Persons with a history of previous hip fractures at the start of follow-up were excluded to ascertain truly incident hip fractures. However, this may have underestimated the risk of hip fractures during antipsychotic use; ie, those subjects who had experienced previous hip fractures could well be more susceptible to antipsychotic-induced hip fractures.

Although registers do not reveal whether the purchased drugs are actually consumed, the validity of the Finnish Prescription Register in measuring exposure to antipsychotics among older persons has been previously confirmed.[41] The Prescription Register does not include information on prescribed dose. The strength of our study was its ability to model the duration and dose of antipsychotic use.[16] When interpreting our results of the dose-wise analyses, it is important to remember that the dose represents the average dose during the entire period of antipsychotic use. Due to the possible temporal changes in dosage, the dose may not necessarily reflect the dose at any distinct time point, such as the dose at the time when hip fracture occurred.

Although we controlled for many known risk factors of hip fracture that were unevenly distributed between antipsychotic users and nonusers, we did not have information on the indication for antipsychotic use or the severity of behavioral and psychological symptoms and Alzheimer's disease. Thus, we were unable to exclude the effect of possible confounding by indication. The association between antipsychotic use and hip fractures could be confounded by indication, namely behavioral and psychological symptoms such as agitation that may expose persons to higher risk of falling and consequent fractures. The registers utilized in this study lack data on behavioral and psychological symptoms as well as cognitive and physical functioning and frailty, all of which could affect the risk of both antipsychotic use and hip fractures. Some previous studies[42,43] have determined the magnitude of the effect of these factors in the association between psychotropic drug use and hip fractures. Both reports concluded that, although the risk estimates were overestimated, the association was still significant after correction of the bias, and no factors were found that could explain the entire magnitude of the association. We adjusted our analyses for time-dependent use of other psychotropic drugs, as these have been associated with an increased risk of hip fracture. It is also likely that concomitant use of multiple psychotropic drugs is a strong marker of more severe or more frequent behavioral and psychological symptoms; ie, an individual displaying intense agitation, anxiety, or both is likely to be prescribed more than 1 sedating drug. Analyses comparing users of different antipsychotics are less impacted by confounding by indication, as all users have some indication for antipsychotic use. In these analyses, we found no difference in the risk associated with quetiapine compared with risperidone for the first 2.7 years of use despite possible differences in indications of use. Furthermore, the finding of a dose-response relationship in risperidone use is interpreted as evidence of true drug effects instead of confounding.

CONCLUSION

Antipsychotic use was associated with an increased risk of hip fracture among community-dwelling persons with Alzheimer's disease. The risk was increased from the first days of use and remained elevated with long-term use. No differences were found in the risk of hip fracture between quetiapine and risperidone during the first 2 years of use. Our results highlight the need for a high threshold for prescribing antipsychotics to individuals with Alzheimer's disease.

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Drug names: aripiprazole (Abilify and others), olanzapine (Zyprexa and others), prochlorperazine (Procomp and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).
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Janssen-Cilag, Lundbeck, and Organon; has received fees for giving expert opinions to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer; has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer; has received a grant from Stanley Foundation and Sigrid Jusélius Foundation; and is an advisory board member of AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka. **Drs Taipale**, **Tolppanen**, **Ahonen**, and **Hartikainen**; **Mss Koponen** and **Lavikainen**; and **Mr Tanskanen** have no conflicts of interest to report.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Antipsychotic Use and the Risk of Hip Fracture Among Community-Dwelling Persons With Alzheimer's Disease

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List of Supplementary Material for the article

1. eAppendix 1 Number of Hip Fractures Among Users of Individual Antipsychotic Drugs

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eAppendix 1. Number of Hip Fractures among Users of Individual Antipsychotic Drugs

Antipsychotic drug	Number of users	Person years of use	Number of hip fractures
Risperidone	10,630	8933.4	272
Quetiapine	4,990	5343.9	143
Haloperidol	597	305.3	8
Olanzapine	249	232.2	9
Melperone	198	155.0	3
Perphenazine	127	107.9	4
Levomepromazine	57	43.4	0
Periciazine	39	29.2	1
Flupentixol	28	24.3	3
Sulpiride	23	15.5	0
Aripiprazole	10	6.9	0
Zuclopenthixol	7	2.4	1
Chlorprotixene	6	6.7	0
Chlorpromazine	5	1.7	0
Clozapine	3	2.0	0
Dixyrazine	2	0.3	0
Ziprasidone	1	0.5	0