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Association Between Antidepressant Drug Use and Hip Fracture in Older People Before and After Treatment Initiation

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IMPORTANCE Treatment with antidepressants has been associated with hip fracture. This association could restrict the treatment options, especially in older patients.

OBJECTIVE To investigate the association between antidepressant drug treatment and hip fracture starting 1 year before the initiation of treatment.

DESIGN, SETTING, AND PARTICIPANTS In this nationwide cohort study, 204 072 individuals in the Prescribed Drugs Register of Sweden's National Board of Health and Welfare aged 65 years or older who had a prescription of antidepressants filled between July 1, 2006, and December 31, 2011, were matched by birth year and sex to 1 control participant who was not prescribed antidepressants (for a total of 408 144 people in the register). Outcome data were collected from 1 year before to 1 year after the index date (date of prescription being filled). Data analysis was performed from July 1, 2005, to December 31, 2012.

EXPOSURES First filled prescription of an antidepressant drug.

MAIN OUTCOMES AND MEASURES Incident hip fractures occurring in the year before and year after initiation of antidepressant therapy were registered. Associations were investigated using multivariable conditional logistic regression models and flexible parametric models.

RESULTS Of the 408 144 people in the register who were included in the study, 257 486 (63.1%) were women, with a mean (SD) age of 80.1 (7.2) years. Antidepressant users sustained more than twice as many hip fractures than did nonusers in the year before and year after the initiation of therapy (2.8% vs 1.1% and 3.5% vs 1.3%, respectively, per actual incidence figures). In adjusted analyses, the odds ratios were highest for the associations between antidepressant use and hip fracture 16 to 30 days before the prescription was filled (odds ratio, 5.76; 95% CI, 4.73-7.01). In all separate analyses of age groups, of men and women, and of individual antidepressants, the highest odds ratios were seen 16 to 30 days before initiation of treatment, and no clear dose-response relationship was seen.

CONCLUSIONS AND RELEVANCE The present study found an association between antidepressant drug use and hip fracture before and after the initiation of therapy. This finding raises questions about the association that should be further investigated in treatment studies.

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Supplemental content

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Depression is a common illness among individuals of all ages, with a lifetime prevalence of up to 20% and currently affecting more than 300 million people worldwide.[1-3] Depression is associated with many comorbidities and adversities and is ranked by the World Health Organization as the single largest contributor to global disability.[2,4-6] Antidepressant drugs are a cornerstone for the treatment of depression, but their use is associated with adverse events, especially in old age.[7,8] One of these adverse events is an increased risk of falls.[9] Injurious falls occur more frequently with advancing age and lead to many complications, including the common and serious complication of hip fracture.[10-13] There is also some evidence that antidepressants might affect bone metabolism, thereby increasing the risk of hip fracture.[14,15] A growing body of research has established associations between the use of most groups of antidepressants and hip fracture among older people.[7,16-20] All such studies, however, have been observational, resulting in debate about causality, confounding, and bias.[21,22]

In particular, individuals with severe diseases and concomitant depression may have an increased risk of fracture before the initiation of antidepressant therapy. In the present Swedish nationwide matched cohort study, we investigated the association between antidepressant therapy and hip fracture in the year before and year after the initiation of treatment among individuals aged 65 years and older.

Key Points

Question Is there an association between antidepressants and hip fracture?

Findings In this population-based, matched cohort study of 408 144 individuals aged 65 years and older, the association between antidepressant drug use and hip fracture was present in the year before and year after the initiation of treatment. The pattern was consistent for all studied antidepressants and subgroups.

Meaning These findings raise questions about the association between antidepressant drug use and hip fracture that requires further analysis in treatment studies.

Methods

Study Cohort

Participants were selected using the Prescribed Drugs Register of Sweden's National Board of Health and Welfare, which contains data on all drug prescriptions issued since July 1, 2005. All individuals aged 65 years and older who had a prescription for an antidepressant drug filled between July 1, 2006, and December 31, 2011, were selected for the study. All drugs belonging to group N06A in the Anatomical Therapeutic Chemical classification system were considered to be antidepressant drugs. To reduce the risk of bias related to recent antidepressant drug use, we included only individuals who had not been prescribed antidepressants for at least 1 year. Each participant was matched to 1 individual who did not use antidepressants during the study period, based on sex and year of birth. The study cohort consisted of 204 072 cases and the same number of controls. Data analysis was conducted between July 1, 2005, and December 31, 2012.

This study was approved by the Regional Ethical Review Board in Umeå, Sweden, and by the National Board of Health and Welfare in Sweden. The requirement for informed consent was waived by both institutions.

Outcome and Data Sources

Additional information was collected from other national registers. Diagnostic codes, registered according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*), were retrieved from the National Patient Register, which includes data from inpatient care since the 1960s and specialist outpatient visits since 2001. The National Patient Register does not include diagnoses from primary care services. Data on socioeconomic status, including educational level, marital status, and early retirement, were collected from Statistics Sweden. Dates of death were retrieved from the National Death Registry.

Baseline data were collected at the index date, which was set as the date of the prescription being filled. The outcome variable, hip fracture, was defined to include all events registered as *ICD-10* codes S72.0 (fracture of head and neck of femur), S72.1 (pertrochanteric fracture), and S72.2 (subtrochanteric fracture of femur). Outcome data were collected from 1 year before to 1 year after the index date. Analyses included the incidents most closely preceding and following the index date, with a maximum of 2 recorded incidents of hip fracture for each participant.

Statistical Analysis

Several analytical methods were used to examine the association between the use of antidepressants and hip fracture. We investigated whether the association was time dependent using Schoenfeld residuals. After determining that the association was time dependent, we used flexible parametric models for the survival analysis, which, unlike Cox proportional hazards regression models, allow time-dependent covariates. Retrospective and prospective hip fractures were analyzed independently using 3 *df* and knots at default positions.[23] The analyses were conditional and thus adjusted for sex and age, but no other adjusting variable was used.

To investigate the range of associations, conditional logistic regression models for 10 different time frames were used. Associations were analyzed during days 1 to 15, 16 to 30, 31 to 90, 91 to 183, and 183 to 365 after the index date and during the corresponding time frames before the initiation of treatment. In all analyses, each participant who had a hip fracture or had died in any time frame closer to the index date was excluded along with their matched individual. Ninety days after the last prescription was filled, participants were excluded from further analyses. Participants whose treatment was switched from one antidepressant to another remained

in the analyses (n = 5903). To investigate possible sex differences, separate analyses were conducted for men and women, and the interaction term sex × antidepressant was inserted in unconditional logistic regression models.

Separate analyses were performed for the 3 most commonly prescribed antidepressants: citalopram hydrobromide (ATC code N06AB04), mirtazapine (N06AX11), and amitriptyline hydrochloride (N06AA09). The association among the oldest old (aged ≥85 years) was analyzed separately, and interaction effects were evaluated using the term age group × antidepressant, as this age group is considered to be more sensitive than younger groups to adverse drug effects.

The simple regression analyses were adjusted for sex and age through the matching process. Multivariable regression analyses were conducted to adjust for conditions possibly affecting the association between antidepressant treatment and hip fracture. Variables were chosen based on scientifically established associations and our clinical experience. Prospective analyses were adjusted for conditions present at the index date, whereas conditions present 1 year before the index date were included in the retrospective analyses. All variables are presented in **Table 1**.

To investigate whether the association between antidepressant drug use and hip fracture was dose dependent, comparisons were made between users of high vs low doses of all antidepressants and of citalopram, mirtazapine, and amitriptyline separately. Most prescriptions were for the recommended starting doses of the drugs. Hence, the starting dose and lower doses were classified as low, and all doses exceeding the recommended starting dose were classified as high. Simple and multivariable unconditional logistic regression models were used, and the cohort not receiving antidepressants was not included in these analyses. Data on dose were unavailable for 4007 participants, and these individuals were excluded from these analyses.

P values ≤.05 were considered to be significant; testing was 2-tailed and unpaired. Statistical analyses were performed using SPSS, version 23.0, for Macintosh (IBM Corp) and Stata, version 12 for Macintosh (StataCorp) software.

Results

Participant Characteristics

The matched cohort of 408 144 people (204 072 cases and as many controls) had a mean (SD) age of 80.1 (7.2) years, and 257 486 (63.1%) were women.

The most commonly used antidepressants were selective serotonin reuptake inhibitors, making up 62.6% of the antidepressant drugs used. Sex differences were seen in many background variables; women were older and more often widowed than were men. Men had a higher prevalence of most diagnoses, but women sustained more hip fractures. Individuals who started antidepressant treatment had more than twice as many incidents of hip fracture, before (5642 vs 2189) and after (7137 vs 2625) the initiation of treatment than did those

Table 1. Characteristics of All Participants

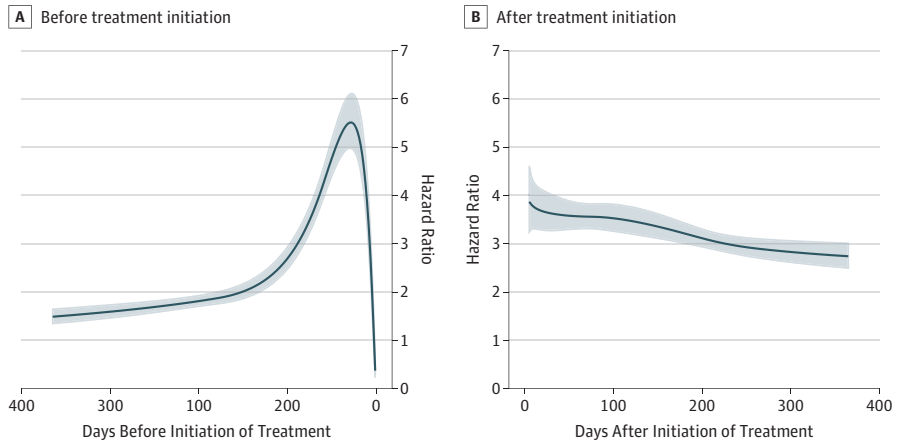
Characteristic	At Index Date (n = 408 144), %	1 y Before (n = 408 144), %
Age, mean (SD), y	80.1 (7.2)	79.1 (7.2)
Highest educational level[a]		
Unspecified	2.0	NA
Primary school	54.1	
Secondary school, 2 y	23.6	
Secondary school, 3 y	7.0	
University	13.3	
Marital status[a]		
Married	49.5	NA
Unmarried	6.9	
Divorced	12.6	
Widowed	31.1	
Early retirement (age <65 y)[a]	1.4	NA
Medical conditions[b]		
Alcohol intoxication, ever	2.0	1.8
Chronic obstructive pulmonary disease	4.2	3.4
Dementia	4.7	2.7
Depression, ever	2.6	1.4
Diabetes	11.1	9.6
Hemorrhagic stroke, ever	1.5	1.0
Ischemic stroke, ever	10.5	7.5
Kidney failure, ever	1.9	1.2
Malignant disease, ever	23.3	21.0
Myocardial infarction, ever	9.8	8.5
Drug use		
Antidepressant drug classes (ATC code)		NA
Tricyclic antidepressants (N06AA)	6.7	
SSRIs (N06AB)	31.3	
Other antidepressants (N06AX)	12.0	
Individual antidepressants		NA
Amitriptyline (N06AA09)	6.4	
Citalopram (N06AB04)	25.5	
Sertraline (N06AB06)	5.0	
Mirtazapine (N06AX11)	9.3	
Other drugs		
Antidementia drugs, after 2005 (N06D)	4.3	2.8
Antipsychotics, current use (N05A)	1.2	0.4
Benzodiazepines, after 2005 (N05BA)	7.5	7.0
Bisphosphonates, current use (M05BA)	5.2	4.7
Prednisolone, current use (H02AB06)	7.0	5.8
Hip fracture incidence, No. (%)		
≤365 d before initiation of treatment	7831 (1.9)	NA
≤365 d after initiation of treatment	9762 (2.4)	NA

Abbreviations: ATC, Anatomical Therapeutic Chemical; NA, not applicable; SSRI, selective serotonin reuptake inhibitor.

[a] Investigated only at the index date.

[b] Medical conditions are registered dichotomously and include only those registered in specialized care.

Figure. Associations Between Antidepressant Drug Treatment Initiation and Hip Fracture



Flexible parametric models for all participants and all antidepressants before (A) and after (B) treatment initiation. Nonusers of antidepressants are the reference in the analyses. Conditional analyses were performed using 3 *df* and knots at default positions. The gray area represents the 95% CI. Participants who had a hip fracture, died, or stopped filling their prescription were censored from the analysis.

Table 2. Multivariable Conditional Logistic Regression Model Associations Between Antidepressant Drug Initiation and Hip Fracture[a]

Time Frame	OR (95% CI) All Participants (N = 408 144)	Men (n = 150 658)	Women (n = 257 486)	Interaction *P* Value
Before initiation of treatment, d				
183-365	1.59 (1.46-1.74)	1.87 (1.57-2.22)	1.51 (1.36-1.66)	.02
92-182	2.20 (1.98-2.45)	2.31 (1.87-2.86)	2.16 (1.91-2.45)	.26
31- 91	4.14 (3.71-4.61)	4.86 (3.91-6.04)	3.90 (3.44-4.42)	.08
16-30	5.76 (4.73-7.01)	9.38 (6.11-14.40)	4.82 (3.85-6.02)	.006
1-15	2.27 (1.85-2.78)	2.51 (1.72-3.65)	2.16 (1.70-2.76)	.44
After initiation of treatment, d				
1-15	3.36 (2.76-4.09)	6.15 (4.08-9.29)	2.70 (2.15-3.38)	.02
16-30	3.56 (2.88-4.41)	5.93 (3.67-9.60)	3.09 (2.44-3.91)	.11
31-91	2.90 (2.59-3.25)	3.20 (2.57-4.00)	2.78 (2.44-3.17)	.07
92-182	3.20 (2.85-3.58)	3.76 (2.97-4.77)	3.01 (2.65-3.43)	.03
183-365	2.54 (2.32-2.78)	2.50 (2.08-2.99)	2.56 (2.30-2.84)	.45

Abbreviation: OR, odds ratio.

[a] Nonusers of antidepressants are the reference in all analyses. All conditional models were adjusted for sex and age through matching. All analyses were adjusted for marital status, level of education, and early retirement at the index date. All prospective analyses were adjusted for renal failure, chronic obstructive pulmonary disease, malignant disease, alcohol intoxication, depression, diabetes, myocardial infarction, ischemic stroke, hemorrhagic stroke, dementia, and the use of antidementia drugs, antipsychotic drugs, benzodiazepines, bisphosphonates, and prednisolone at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. In each analysis, each participant who had a hip fracture, had died, or stopped filling their prescription in any time frame closer to the index date was excluded along with their matched individual (at the most, n = 140 608) in the time frame 183 to 365 days after initiation of treatment in all participants. The interaction term sex × antidepressant was analyzed in multivariable unconditional logistic regression models using the same variables as in the conditional analyses, as well as sex and age.

who did not use antidepressant drugs (Table 1; eTable 1 and eTable 2 in the Supplement).

Associations Between Antidepressant Drug Use and Hip Fracture

The association between any antidepressant drug use and hip fracture in the total cohort is shown in the **Figure**. Antidepressant users had an increased incidence of hip fracture before and after the initiation of treatment (peak hazard ratio [HR], 5.5; 95% CI, 4.9-6.1). The curve reveals a gradually increasing hazard ratio, which peaked in the month before the initiation of therapy and then fell gradually until 1 year after the index date.

These results were confirmed by evaluation of the association using conditional logistic regression models for 5 time frames before and the corresponding 5 time frames after the initiation of treatment (**Table 2**). The odds ratio (OR) for the association between any antidepressant drug use and hip fracture peaked 16 to 30 days before the initiation of treatment (OR, 5.76; 95% CI, 4.73-7.01), with the second highest peak occurring 31 to 91 days before treatment initiation (OR, 4.14; 95% CI, 3.71-4.61).

Subgroup Analyses

The OR for the association between antidepressant use and hip fracture was highest at 16 to 30 days before treatment initia-

Table 3. Multivariable Conditional Logistic Regression Model Associations Between Antidepressant Drug Initiation and Hip Fracture in Subgroups[a]

Time Frame	Medication, OR (95% CI)			Age, OR (95% CI)		Interaction *P* Value
	Citalopram (n = 208 214)	Mirtazapine (n = 76 080)	Amitriptyline (n = 52 550)	65-84 y (n = 298 022)	≥85 y (n = 110 122)	
Before initiation of treatment, d						
183-365	1.65 (1.48-1.85)	1.74 (1.43-2.10)	1.36 (1.02-1.82)	1.53 (1.35-1.73)	1.61 (1.43-1.81)	.47
92-182	2.33 (2.01-2.70)	2.68 (2.13-3.36)	0.88 (0.61-1.27)	2.19 (1.86-2.57)	2.16 (1.87-2.49)	.25
31-91	4.09 (3.54-4.73)	6.74 (5.27-8.61)	1.91 (1.36-2.69)	3.92 (3.34-4.61)	4.19 (3.63-4.84)	.77
16-30	5.47 (4.20-7.13)	8.54 (5.70-12.80)	3.95 (1.77-8.80)	5.68 (4.27-7.56)	5.73 (4.37-7.51)	.97
1-15	2.04 (1.55-2.69)	4.75 (3.00-7.54)	1.26 (0.68-2.36)	2.67 (1.94-3.67)	2.01 (1.55-2.62)	.12
After initiation of treatment, d						
1-15	3.15 (2.43-4.09)	6.20 (3.83-10.06)	2.04 (1.10-3.78)	3.59 (2.67-4.83)	3.16 (2.43-4.12)	.43
16-30	3.47 (2.64-4.54)	4.89 (2.94-8.16)	2.95 (1.44-6.04)	3.14 (2.29-4.30)	3.80 (2.86-5.04)	.55
31-91	3.21 (2.77-3.71)	2.56 (1.94-3.39)	1.55 (1.09-2.22)	2.64 (2.23-3.12)	3.06 (2.63-3.56)	.46
92-182	3.88 (3.34-4.51)	2.61 (2.00-3.40)	1.80 (1.17-2.78)	3.50 (2.94-4.16)	2.85 (2.45-3.30)	<.001
183-365	2.93 (2.60-3.30)	2.10 (1.69-2.62)	2.17 (1.55-3.03)	2.92 (2.55-3.33)	2.18 (1.93-2.46)	<.001

Abbreviation: OR, odds ratio.

[a] Nonusers of antidepressants are the reference in all analyses. All conditional models were adjusted for sex and age through matching. All analyses were adjusted for marital status, level of education, and early retirement at the index date. All prospective analyses were adjusted for renal failure, chronic obstructive pulmonary disease, malignant disease, alcohol intoxication, depression, diabetes mellitus, myocardial infarction, ischemic stroke, hemorrhagic stroke, dementia, and the use of antidementia drugs, antipsychotic drugs, benzodiazepines, bisphosphonates and prednisolone at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. In each analysis, each participant who had a hip fracture, had died, or stopped filling their prescription in any time frame closer to the index date was excluded along with their matched individual, at the most n = 97 291, in the time frame 183-365 days after initiation of treatment in the subcohort aged 65 to 84 years, and n = 63 400 in the citalopram subcohort. The interaction term age group × antidepressant was analyzed in unconditional regression models using the same variables as in the conditional analyses, as well as sex.

tion in men (OR, 9.38; 95% CI, 6.11-14.40) and in women (OR, 4.82; 95% CI, 3.85-6.02). The ORs for the association were higher among men than among women (significant sex × antidepressant interaction) in 4 time frames (Table 2).

Similar patterns of association between antidepressant drug use and hip fracture were seen for participants aged 65 to 84 years and older and participants aged 85 years and older. In both age groups, the OR for the association was highest at 16 to 30 days before the initiation of treatment (OR, 5.68; 95% CI, 4.27-7.56 and OR, 5.73; 95% CI, 4.37-7.51, respectively). However, the OR for the association was higher in the younger cohort at 92 to 182 (OR, 3.50; 95% CI, 2.94-4.16) and 183 to 365 days after the initiation of treatment (OR, 2.92; 95% CI, 2.55-3.33) (significant age group × antidepressant interaction) (**Table 3**).

In separate analyses of the 3 most commonly used antidepressant drugs (citalopram, mirtazapine, and amitriptyline), the ORs also peaked 16 to 30 days before the initiation of treatment (OR, 5.47; 95% CI, 4.20-7.13; OR, 8.54; 95% CI, 5.70-12.80; and OR, 3.95; 95% CI, 1.77-8.80, respectively). The citalopram and mirtazapine analyses revealed associations between the initiation of antidepressant treatment at baseline and the incidence of hip fracture in all time frames. For amitriptyline, the association was significant in 8 of the 10 time frames.

Analyses of Higher vs Lower Doses

Results of the unconditional multivariable regression analyses of higher vs lower dose are presented in **Table 4**. The study of all antidepressants showed increased odds of hip fracture associated with higher doses of antidepressants in 2 of the 10 time frames, peaking at 16 to 30 days before the initiation of treatment (OR, 1.47; 95% CI, 1.26-1.72), and lower odds in 1 time frame (OR, 0.87; 95% CI, 0.78-0.97). Higher doses of citalopram were associated with increased odds of hip fracture 16 to 30 days before treatment initiation (HR, 1.32; 95% CI, 1.26-1.72) and decreased odds in 2 other time frames (HR, 0.66; 95% CI, 0.58-0.76; and HR, 0.82; 95% CI, 0.70-0.96). Higher doses of mirtazapine were associated with increased odds of hip fracture at 16 to 30 days before treatment initiation (HR, 1.65; 95% CI, 1.25-2.18), but not in any other time frame. The amitriptyline analysis revealed no significant difference between users of higher and lower doses.

The results of all simple regression models as well as the characteristics of subgroups of the cohort and sensitivity analyses of the subcohorts with dementia and depression are reported in eTables 1-7 in the Supplement. These data show similar patterns of association as the main results presented above.

Discussion

In this nationwide matched cohort study of older people in Sweden, participants prescribed antidepressant drugs had more comorbidities and sustained more than twice as many hip fractures than did those who did not receive antidepressants. However, the increased incidence was almost identical before and after the initiation of treatment, with the highest ORs for associations observed at 16 to 30 days before the prescription was filled. The ORs for the associations increased from 1 year before the index date, peaked close to this date, and then fell until 1 year thereafter. The associations had similar patterns in women and men, but the ORs were slightly higher in men. No clear dose-response relationship was seen. The differences between unadjusted results and those of the multi-

Table 4. Multivariable Unconditional Logistic Regression Model Associations Between Antidepressant Drug Initiation and Hip Fracture by Dose, Higher vs Lower Doses[a]

Time Frame	OR (95% CI)			
	All Antidepressants (N = 200 065)	Citalopram[b] (n = 104 026)	Mirtazapine[c] (n = 35 382)	Amitriptyline[d] (n = 26 275)
Before initiation of treatment, d				
183-365	0.87 (0.78-0.97)[e]	0.66 (0.58-0.76)[e]	1.19 (0.93-1.53)	1.13 (0.75-1.71)
92-182	0.90 (0.80-1.02)	0.82 (0.70-0.96)[e]	0.97 (0.74-1.28)	0.85 (0.47-1.54)
31-91	1.09 (0.99-1.21)	1.01 (0.89-1.15)	1.06 (0.86-1.30)	1.17 (0.76-1.81)
16-30	1.47 (1.26-1.72)[e]	1.32 (1.07-1.63)[e]	1.65 (1.25-2.18)[e]	1.53 (0.71-3.30)
1-15	1.00 (0.80-1.25)	0.87 (0.64-1.19)	1.28 (0.86-1.92)	0.98 (0.39-2.47)
After initiation of treatment, d				
1-15	0.87 (0.72-1.04)	0.93 (0.73-1.18)	0.68 (0.46-1.01)	1.44 (0.70-2.98)
16-30	1.29 (1.08-1.55)[e]	1.19 (0.95-1.49)	1.42 (0.92-2.18)	0.60 (0.23-1.56)
31-91	1.04 (0.94-1.16)	0.94 (0.83-1.06)	0.81 (0.61-1.08)	1.29 (0.81-2.06)
92-182	1.03 (0.93-1.14)	0.90 (0.79-1.02)	0.95 (0.73-1.25)	0.96 (0.54-1.68)
183-365	0.99 (0.91-1.08)	0.91 (0.81-1.01)	0.94 (0.75-1.18)	1.18 (0.79-1.76)

Abbreviation: OR, odds ratio.

[a] Users of lower doses are the reference in all analyses. All analyses were adjusted for sex, age, marital status, level of education, and early retirement at the index date. All prospective analyses were adjusted for renal failure, chronic obstructive pulmonary disease, malignant disease, alcohol intoxication, depression, diabetes, myocardial infarction, ischemic stroke, hemorrhagic stroke, dementia, and the use of antidementia drugs, antipsychotic drugs, benzodiazepines, bisphosphonates, and prednisolone at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. In each analysis, each participant who had a hip fracture, had died, or stopped filling their prescription in any time frame closer to the index date was excluded (at the most, n = 66 541) in the time frame 183 to 365 days after initiation of all antidepressants.

[b] Citalopram low dose (n = 49 348): mean, 10.0 mg; median, 10.0 mg (range, 10.0-10.0 mg); high dose (n = 54 678): mean, 20.1 mg; median, 20.0 mg (range, 20.0-40.0 mg).

[c] Mirtazapine low dose (n = 23 474): mean, 15.0 mg; median, 15.0 mg (range, 15.0-15.0); high dose (n = 11 908): mean, 30.4 mg; median, 30.0 mg (range, 30.0-45.0 mg).

[d] Amitriptyline low dose (n = 19 729): low dose, 10.0 mg; median, 10.0 mg (range, 10.0-10.0); high dose (n = 6546): mean, 25.8 mg; median, 25.0 mg (range, 25.0-50.0 mg).

[e] Statistically significant.

variable regression models were small, which was unexpected considering the wide range of covariates included in the analyses.

Previous Research

Associations between antidepressant drugs and injurious falls, as well as hip fracture, have been established in several observational studies.[7,9,16-20,24-26] To our knowledge, only 1 randomized clinical trial has been conducted, and it was underpowered and unable to establish any association between selective serotonin reuptake inhibitor use and falls.[27] Several studies have shown that the risk of falls and fracture is highest soon after the initiation of treatment.[7,19,20,25] One observational study including the period before the initiation of antidepressant treatment revealed a higher incidence of falls not only after initiation but also in the days preceding initiation of treatment.[24] Two studies involved self-controlled case-series analyses that revealed higher incidences of falls and hip fracture during periods of drug treatment, but the periods just before the reinitiation of treatment were not analyzed specifically.[20,25] Based on our results, we suggest that older people with depression have an increased risk of hip fracture before starting antidepressant treatment, owing to a high burden of comorbidity and confounding by indication. To our knowledge, this pretreatment association has not been demonstrated in previous studies, which have shown an increased risk of fracture only after the initiation of therapy.

Although the evidence for a causal relationship between antidepressant use and hip fracture is weak,[21,22] influential bodies advocate against the use of antidepressants in older people. The American Geriatrics Society states in the Beers criteria that antidepressants should be avoided in older people with histories of falling unless safer alternatives are not available.[28] In reports from 2016, Sweden's National Board of Health and Welfare and the Swedish Medical Products Agency state that antidepressant drug use increases the risks of falls and fractures in older people.[29,30]

Relevance and Interpretation

The method used in the present study, which involved comparison of antidepressant users and nonusers, was adopted to compare associations before and after the initiation of antidepressant treatment. Participants who were prescribed antidepressants differed significantly from those who were not in many other aspects. The 2 groups are thus not easily comparable, and adjustment of the analyses for comorbidities and socioeconomic variables made little difference in the results. If we had examined associations starting from the index date, as in many previous observational studies, the conclusion that the association between antidepressant use and hip fracture might be causal would be possible to suggest. However, the retrospective analyses included a nonexposure control period for each case and revealed a higher risk of hip fracture also before the initiation of antidepressant drug use. This finding infers the presence of residual confounding, the size of which can be roughly estimated through comparing time frames with and without the exposure to antidepressant drugs.

The upward-sloping curve of the observed ORs and HRs, which was highest close to the initiation of treatment and then declined again, could represent parallel increases in the risks of hip fracture and of becoming depressed; these factors are not necessarily dependent on each other, but rather may reflect general susceptibility during times of other hardship. Depression may also increase the risk of falling and sustaining hip fracture, as has been suggested previously.[5,31-33] If that risk is greater than that posed by antidepressants, the successful initiation of treatment with subsequent remission from depression would be expected to lead to a lower risk thereafter. Both antidepressant use and depression have been shown to affect bone metabolism, which could contribute to the higher incidence of hip fracture both before and after initiation of treatment.[14,15,34] A possible explanation for the highest ORs 16 to 30 days before the initiation of treatment is that hip fracture requiring hospitalization leads to the accentuation of depressive symptoms, which is acknowledged by hospital staff, who then initiate antidepressant drug treatment. While hospitalized, patients would be less able to attend a pharmacy to have a prescription filled, which could be the reason for the lower ORs 1 to 15 days before the index date.

The ORs for the association between antidepressant drug use and hip fracture were higher in men than in women, especially close to the index date. Several researchers have suggested that depression is underdiagnosed and undertreated in men, and that men are less likely to seek help when depressed.[35-37] Perhaps a greater proportion of untreated depression is recognized in men when they are hospitalized after hip fracture, which would strengthen this association.

Clinical Implications

Even if antidepressant drug use does not increase the risk of hip fracture, the prescription of antidepressants to older people should be restrictive, as the evidence for positive effects is limited.[38,39] Antidepressants are associated with adverse effects other than falls and fractures, including QT interval prolongation, hyponatremia, and gastrointestinal bleeding.[7,8,40] In addition, our findings do not exclude the possibility that antidepressant use is associated with increases in the risk of falling and sustaining a hip fracture. In particular, reasons for the increased risk of hip fracture before and after the initiation of therapy may differ. Regardless, careful initiation of treatment and close monitoring of positive and adverse effects should accompany the prescription of an antidepressant to an elderly person.

Strengths and Limitations

This study has strengths and limitations. One strength is that all people aged 65 years and older in Sweden who filled prescriptions of antidepressant drugs during 2006-2011 were included. As Swedish residents have no other legal means of obtaining antidepressants, this approach minimized selection bias. In addition, this study had nationwide coverage without the application of exclusion criteria, so our results should be generalizable to other populations of older people using antidepressants. All diagnoses from specialized care were available, resulting in little loss of data concerning the outcome of hip fracture.

One limitation is that, because diagnoses established in primary care settings were not available, we expect that our data set was characterized by a significant lack of information concerning comorbidity variables, such as diagnoses of dementia, diabetes, and mild to moderate depression. This also means uncertainty about the indications for antidepressant treatment, which in some cases might have been neuropathic pain, anxiety, sleeping disorders, or behavioral and psychological symptoms of dementia. All analyses were based on the date when the prescription of an antidepressant was filled; some participants may have initiated treatment at later dates or not at all. The definitions of higher and lower doses of antidepressants do not fully correspond to what would be considered high and low therapeutically. Because low starting doses were used in most cases, we had to apply lower cutoff values for statistical purposes. Hence, higher doses than those defined as higher in the present study might show other patterns of association with hip fracture.

Although we merged data from several national registers, the amount of information obtainable through a register study is limited. We know that patients who were prescribed antidepressants differed substantially from the matched controls, but we do not know the extent or how these differences progressed during the 2-year study period. Hence, we did not attempt to calculate the potential additional residual risk posed by the initiation of antidepressant treatment.

Conclusions

In the present study, we found an association between antidepressant drug use and hip fracture. The association was present 1 year before the initiation of treatment and peaked 16 to 30 days before treatment initiation. The pattern was consistent across all studied antidepressants and subgroups. These findings raise questions about associations between antidepressant use and hip fracture seen in previous observational studies. Further analysis of this association in treatment studies and examination of the incidence of hip fracture before and after the discontinuation of treatment are required and may shed further light on the possible residual risk associated with treatment.

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