Conventional or Atypical Antipsychotics and the Risk of Femur Fracture Among Elderly Patients: Results of a Case-Control Study

Rosa Liperoti, M.D., M.P.H.; Graziano Onder, M.D., Ph.D.; Kate L. Lapane, Ph.D.; Vincent Mor, Ph.D.; Joseph H. Friedman, M.D.; Roberto Bernabei, M.D.; and Giovanni Gambassi, M.D.

Objective: Conventional antipsychotics have been linked to an increased risk of femur fracture. Despite a lower propensity of atypical agents to cause gait and movement disorders, a correlation between these medications and the risk of femur fracture remains to be established. The aim of this study was to estimate the effect of atypical and conventional antipsychotics on the risk of hospitalization for femur fracture.

Method: We conducted a case-control study on nursing home residents in 6 U.S. states by using the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, which includes data from the Minimum Data Set linked to Medicare inpatient claims. Cases were residents hospitalized for femur fracture between July 1, 1998, and December 31, 1999. For each case, we identified up to 5 controls residing in the same facility during the same period of time. The sample consisted of 1787 cases and 5606 controls.

Results: After control for potential confounders, the risk of hospitalization for femur fracture was increased for users of atypical (OR = 1.37, 95% confidence interval [CI] = 1.11 to 1.69) and conventional antipsychotics (OR = 1.35, 95% CI = 1.06 to 1.71) relative to nonusers. With respect to individual agents, an excess risk was estimated for risperidone (OR = 1.42, 95% CI = 1.12 to 1.80), olanzapine (OR = 1.34, 95% CI = 0.87 to 2.07), and haloperidol (OR = 1.53, 95% CI = 1.18 to 2.26). No other antipsychotic could be analyzed individually.

Conclusion: Conventional and atypical antipsychotics appear to increase the risk of hospitalization for femur fracture in a population of institutionalized elderly patients. These medications should be used with caution, especially among patients with a high risk of falls.

(J Clin Psychiatry 2007;68:929–934)

Received Aug. 7, 2006; accepted Oct. 16, 2006. From the Center for Medicine of Aging, Department of Gerontology and Geriatrics, Catholic University of the Sacred Heart, Rome, Italy (Drs. Liperoti, Onder, Bernabei, and Gambassi); the Center for Gerontology and Health Care Research, Department of Community Health, Brown University School of Medicine, Providence, R.I. (Drs. Lapane, Mor, and Gambassi); and the NeuroHealth Parkinson's Disease and Movement Disorders Center, Warwick, R.I. (Dr. Friedman).

Funding source: National Institute on Aging, National Institutes of Health, Health Care Financing Administration contract #500-95-0062 Data Use Agreements 8552.

Dr. Friedman is a member of the speakers' or advisory boards for AstraZeneca, Novartis, Ovation, Acadia, and Teva. Drs. Liperoti, Onder, Lapane, Mor, Bernabei, and Gambassi report no other financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Rosa Liperoti, M.D., Centro di Medicina dell'Invecchiamento, Dipartimento di Scienze Gerontologiche, Geriatriche e Fisiatriche, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8 -00168 Rome, Italy (e-mail: rossella_liperoti@rm.unicatt.it).

Antipsychotic drugs, similar to benzodiazepines[1] and antidepressants,[2] have been linked to an increased risk of femur fracture.[3] In 1987, Ray et al.[3] documented that among Medicaid enrollees, conventional antipsychotics were associated with a 2-fold increased risk of femur fracture and that this was dose dependent. Two additional studies aimed at elucidating the role of benzodiazepines and antidepressants on the risk of femur fracture reported that patients also taking antipsychotics were, respectively, 1.6 and 2.8 times more likely to experience a femur fracture than nonusers.[2,4] No information was given on the specific class of antipsychotics by either study.

Conventional antipsychotics can elicit extrapyramidal symptoms (EPS), including parkinsonism with akinesia, rigidity, and unsteady gait. Thus, these medications are thought to be indirectly linked to femur fractures via an increased risk of falling.[5] Atypical antipsychotics, namely clozapine, risperidone, olanzapine, quetiapine, and more recently ziprasidone and aripiprazole, confer a lower risk of all EPS compared with conventional agents.[6] Due to this superior EPS profile, these newer agents are more widely used outside of their approved indications.[7] However, some recently published data have suggested that atypical antipsychotics are not associated with a lower risk of falls compared with conventional agents.[8]

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

To date, no large study has examined the association between the use of atypical antipsychotics and the risk of femur fracture. We therefore conducted a case-control study to estimate the effect of atypical and conventional antipsychotics on the risk of hospitalization for femur fracture among nursing home residents in 6 U.S. states.

METHOD

Data Source

We used the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS).[9,10] The MDS is a standardized, clinically based instrument that collects information on each resident's demographic, functional, medical, psychological, and cognitive status. The Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) require that each Medicare/Medicaid certified nursing home conduct an MDS assessment of all residents upon admission and quarterly thereafter, as well as with any significant change in the resident's status. Since June 22, 1998, the Centers for Medicare and Medicaid Services maintains a centralized repository of all MDS data (version 2.0), and this is used for administrative and research purposes.

Study Population

Data collected in the nursing homes of 6 states, including Ohio, Maine, Illinois, Mississippi, South Dakota, and New York, were used in the current study. Eligible candidates for this study were residents who were at least 65 years of age. Bedridden residents and those with paraplegia, quadriplegia, or cancer were excluded.

Case Selection

The SAGE database links MDS data to the Medicare inpatient claim files (part A), which contain information on residents' health service use. The Medicare inpatient claim data provide the admission diagnosis and up to 10 discharge diagnoses for any hospitalizations, recorded by using the *International Classification of Diseases,* Ninth Revision (ICD-9), codes.[11] We identified cases by inpatient hospitalizations in which the primary discharge diagnosis was femur fracture (ICD-9 codes: 820 through 821). We used the first hospitalization for femur fracture to define case status among persons with multiple hospitalizations. We identified 2938 cases, occurring between July 1, 1998, and December 31, 1999. We finally selected as eligible cases only those residents with an MDS assessment conducted within 120 days prior to hospitalization (N = 2579).

Control Selection

It has been documented that individual as well as facility characteristics may affect the probability of being hospitalized from a nursing home.[12] Therefore, controls were selected from a population of hospitalized residents to provide an appropriate comparison group.[13] We identified potential controls by inpatient hospitalizations in which the primary diagnosis at discharge was for either septicemia (ICD-9 codes: 038–038.9) or gastrointestinal bleeding (ICD-9 codes: 578–578.9) or myocardial infarction (ICD 9 codes: 410–410.9). We identified 8456 potential controls. Also, to minimize facility potential confounding effect, we matched cases and controls within facility. Every case could be matched to a maximum of 5 controls residing within the same facility during the same period randomly selected. We excluded cases for whom we could not identify at least 1 eligible control. The final matched sample consisted of 1787 cases and 5606 controls.

Antipsychotic Exposure

Nursing home staff recorded the drug name, dose, frequency, route of administration, whether the order was scheduled (standing order) or pro re nata (PRN), and the National Drug Code for up to 18 medications taken by the resident in the 7 days before the assessment.

We identified, for any study participant, the most proximal assessment reporting drug information before the hospitalization and defined it as the index assessment. We defined as exposed those residents for whom any antipsychotic use was reported at the index assessment. Among exposed residents, we distinguished users of risperidone; users of olanzapine; users of other atypical antipsychotics, including clozapine and quetiapine; users of conventional agents, including chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, promazine, thioridazine, thiothixene, and trifluoperazine; and users of more than 1 antipsychotic agent. These medications were the only antipsychotic agents available during the period of data acquisition. Exposed residents were also classified as standing order or PRN users, on the basis of whether they were receiving antipsychotics on a scheduled order or as needed. We defined as unexposed those residents for whom no antipsychotic use was reported at the index assessment.

Potential Confounders

Residents' sociodemographic characteristics, including age, gender, and race/ethnicity, along with body mass index, indicators of functional and cognitive status, comorbid conditions, and concurrent drug use were considered as variables potentially confounding the relationship under study. To evaluate functional status, we used the Activities of Daily Living scale,[14] a 7-item, 5-level score based on the resident's performance in 7 areas: dressing, eating, toileting, bathing, locomotion, transferring, and incontinence. These items are included in the MDS. We classified the degree of dependence as

 © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

normal/mild (Activities of Daily Living scale score 0–1), moderate (Activities of Daily Living scale score 2–3), or severe (Activities of Daily Living scale score 4–5). The Cognitive Performance Scale (CPS)[15] was used to measure cognitive status. The CPS is a validated scale embedded in the MDS that ranges from 0 (intact cognition) to 6 (severe dementia) and has a good correlation with the Mini-Mental State Exam.[16] The CPS includes the following MDS items: short-term memory, cognitive skills for daily decision making, ability to be understood by others, self-performance in eating, and comatose status. We categorized cognitive impairment as follows: minimal (CPS score 0–1), moderate (CPS score 2–3) and severe impairment (CPS score 4–6).

Information provided by the MDS active clinical diagnosis section was used to assess residents' comorbid conditions. The validity and accuracy of such diagnoses in the SAGE database have been previously shown.[10] Comorbid conditions that were considered as potential confounders were diabetes, cerebrovascular disease, cataract, glaucoma, anemia, bladder incontinence, osteoporosis, dementia, depression, other psychiatric conditions (schizophrenia and bipolar disorder), Parkinson's disease, behavioral symptoms (wandering, verbally or physically abusive behavior, and socially inappropriate behavior), seizures, and a history of falls in the prior 6 months. We also evaluated concomitant medications, focusing on those that may modulate the risk of femur fracture. These medications included cardiovascular drugs (diuretics, β-blockers, α-blockers, centrally acting antihypertensive drugs), anticonvulsants, benzodiazepines, antidepressants, and antihistamines.

Table 1. Principal Sociodemographic, Functional, and Clinical Characteristics of the Study Population (reported as percentages where not otherwise specified)

Characteristic	Cases (N = 1787)	Controls (N = 5606)
Age, mean, y	84.7	83.0
Gender, female	79.2	74.8
Race/ethnicity		
White, not of Hispanic origin	92.6	90.1
Black, not of Hispanic origin	7.0	9.2
Other	0.4	0.7
Body mass index, mean, kg/m^2	22.6	23.8
Functional impairment (ADL score)		
None/mild (0–1)	16.1	14.3
Moderate (2–3)	54.3	46.9
Severe (4–5)	29.6	38.8
Cognitive deficit (CPS score)		
Mild (0–1)	27.5	28.6
Moderate (2–3)	40.3	42.7
Severe (4–6)	32.2	28.7
Diabetes	21.2	30.9
Cerebrovascular disease	18.9	24.8
Cataract	13.0	13.4
Glaucoma	8.3	7.7
Anemia	20.4	24.9
Bladder incontinence	45.7	48.6
Osteoporosis	15.4	11.2
Dementia[a]	49.7	43.3
Depression	34.0	31.5
Other psychiatric conditions[b]	15.6	14.6
Parkinson's disease	7.8	6.7
Behavioral symptoms[c]	21.0	16.2
Seizures	5.7	6.1
History of falls	35.2	24.9

[a]Including Alzheimer's disease, vascular dementia, and other dementia.
[b]Including bipolar disorder and schizophrenia.
[c]Including wandering, verbally or physically abusive behavior, and socially inappropriate behavior.
Abbreviations: ADL = Activities of Daily Living scale, CPS = Cognitive Performance Scale.

Analytic Plan

Sociodemographic, functional, cognitive, and clinical characteristics as well as concomitant drug use of cases and controls were compared. We used conditional logistic regression models to quantify the effect of antipsychotic use on the likelihood of hospitalization for femur fracture, simultaneously controlling for all potential confounders. In a first model, exposure status was categorized as follows: standing order atypical use, PRN atypical use, standing order conventional use, PRN conventional use, and use of more than 1 antipsychotic, with no antipsychotic use as the reference category. A second model was fitted to analyze the effect of individual agents using the following exposure categorization: standing order risperidone use, PRN risperidone use, standing order olanzapine use, PRN olanzapine use, standing order other atypical use, PRN other atypical use, standing order haloperidol use, PRN haloperidol use, standing order other conventional use, PRN other conventional use, and use of more than 1 antipsychotic, with no use as the reference category. All potential confounders were included in the models as categorical variables except age and body mass index, which were analyzed as continuous variables. The use of many covariates in the logistic regression models was done in accordance to recommended analytic standards.[17] We derived crude and adjusted odds ratios (ORs) along with 95% confidence intervals (CIs) from these models. We interpreted the odds ratios as estimates of the relative risk. Statistical analysis was performed using SAS statistical software, version 8 (SAS Institute Inc., Cary, N.C.).

RESULTS

Cases and controls did not differ substantially with respect to age, gender, race/ethnicity, and body mass index (Table 1). Cases were less likely than residents in the control group to present with a severe functional impairment (29.6% vs. 38.8%). There was no main difference with respect to cognitive impairment between cases and controls. Comorbidities were equally distributed in the 2 groups except for a higher prevalence of osteoporosis (15.4% vs.

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

Table 2. Medication Use in the Study Population (reported as percentage)

Medication	Cases (N = 1787)	Controls (N = 5606)
Cardiovascular drugs[a]	48.8	53.7
Anticonvulsants	10.3	10.0
Benzodiazepines	17.1	14.0
Antidepressants	37.1	31.3
Antihistamines	15.6	16.2
Atypical antipsychotics	11.6	8.4
Conventional antipsychotics	9.2	7.6
> 1 antipsychotic	1.0	0.8

[a]Including diuretics, β-blockers, α-blockers, and centrally acting antihypertensive drugs.

Table 3. Drug Regimens Among Antipsychotic Users

Antipsychotic	Number of Prescriptions	Standing Orders, %	Daily Dose, Mode, mg	Daily Dose, Range, mg
Atypical				
Clozapine	18	100	25.0	12.5–200.0
Olanzapine	220	100	5.0	2.5–20.0
Quetiapine	58	100	25.0	25.0–300.0
Risperidone	615	99	1.0	0.5–4.0
Conventional				
Chlorpromazine	44	97	50.0	20.0–150.0
Chlorprothixene	7	99	…	…
Fluphenazine	27	100	2.5	0.5–7.5
Haloperidol	352	88	1.0	0.5–6.0
Loxapine	20	99	10.0	5.0–50.0
Mesoridazine	5	99	20.0	10.0–30.0
Molindone	6	100	5.0	5.0–60.0
Perphenazine	88	98	2.0	2.0–8.0
Promazine	56	97	100.0	…
Thioridazine	140	93	10.0	10.0–100.0
Thiothixene	22	98	2.0	1.0–6.0
Trifluoperazine	8	100	2.0	1.0–8.0

Symbol: … = not available.

11.2%) and a lower prevalence of cerebrovascular disease (18.9% vs. 24.8%) and diabetes (21.2% vs. 30.9%) among cases compared with controls. Relative to controls, cases were more likely to be diagnosed with dementia (49.7% vs. 43.3%) or depression (34.0% vs. 31.5%) and to show behavioral symptoms (21.0% vs. 16.2%). Also more cases than controls had a history of falls in the prior 6 months (35.2% vs. 24.9%).

Table 2 illustrates the use of concomitant medications. Cases were less likely to use cardiovascular drugs than controls (48.8% vs. 53.7%). Finally, cases were more likely to use antidepressants (37.1% vs. 31.3%) and benzodiazepines (17.1% vs. 14.0%) relative to controls, whereas the use of other psychotropic medications, including anticonvulsants and antihistamines, was equally distributed among the 2 groups. There was a difference in the overall prevalence of antipsychotic use (21.8% among cases and 16.8% among controls). Relative to controls, cases were more likely to be prescribed both atypical (11.6% vs. 8.4%) and conventional antipsychotics (9.2% vs. 7.6%).

Table 4. Crude, Adjusted Odds Ratios and 95% Confidence Intervals of Being Hospitalized for Femur Fracture Among Residents Using Antipsychotics on a Standing Order[a] Compared With Nonusers

Antipsychotic	Crude OR	Adjusted OR[b]	95% CI
Atypicals	1.53	1.37	1.11 to 1.69
Risperidone	1.61	1.42	1.12 to 1.80
Olanzapine	1.52	1.34	0.87 to 2.07
Other atypicals[c]	1.07	1.03	0.47 to 2.28
Conventionals	1.46	1.35	1.06 to 1.71
Haloperidol	1.65	1.53	1.18 to 2.26
Other conventionals[d]	1.16	1.09	0.78 to 1.52
More than one antipsychotic agent	1.70	1.59	0.58 to 3.14

[a]Data for pro re nata (PRN) users are not shown.
[b]Adjusted for age, gender, race/ethnicity, body mass index, Activities of Daily Living scale score, Cognitive Performance Scale score, diabetes, cerebrovascular disease, cataract, glaucoma, anemia, bladder incontinence, osteoporosis, dementia, depression, other psychiatric conditions, Parkinson's disease, behavioral symptoms, seizures, history of falls in the prior six months, and concomitant drug use including cardiovascular drugs, anticonvulsants, benzodiazepines, antidepressants, and antihistamines.
[c]Including clozapine and quetiapine.
[d]Including chlorpromazine, chlorprothixene, fluphenazine, loxapine, mesoridazine, molindone, perphenazine, promazine, thioridazine, thiothixene, and trifluoperazine.

Drug regimens among antipsychotic users are shown in Table 3. Among atypical antipsychotics, risperidone was the most commonly prescribed agent accounting for over 60% of prescriptions followed by olanzapine. Haloperidol was the most commonly used agent among conventional antipsychotics (nearly 50% of prescriptions), followed by thioridazine.

After control for potential confounders, the risk of hospitalization for femur fracture was increased for users of atypical (OR = 1.37, 95% CI = 1.11 to 1.69) and conventional antipsychotics (OR = 1.35, 95% CI = 1.06 to 1.71) relative to nonusers (Table 4). With respect to individual agents, an excess risk was estimated for risperidone (OR = 1.42, 95% CI = 1.12 to 1.80), olanzapine (OR = 1.34, 95% CI = 0.87 to 2.07), and haloperidol (OR = 1.53, 95% CI = 1.18 to 2.26). Due to the low prevalence of use, no other antipsychotic, including clozapine, quetiapine, and conventionals other than haloperidol, could be analyzed individually.

Data for PRN users are not reported due to the low prevalence of PRN use (less than 1% of atypical prescriptions and less than 8% of conventional prescriptions).

DISCUSSION

The findings of this study show that the use of conventional and atypical antipsychotics may be associated with an increased risk of hospitalization for femur fracture among nursing home residents. The estimated effect of conventional antipsychotics is consistent with previous evidence from observational studies.[3,5] Also, our findings

 © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

are in accordance with results of a recent observational study on residents of aged care facilities in Australia showing a similar 35% to 70% increase in the risk of falls associated with the use of either atypical or conventional antipsychotics.[8]

In contrast, evidence from clinical trials reporting the rate of falls among dementia patients on atypical antipsychotics did not show an increased risk associated with the use of risperidone compared with placebo.[18–20] Nonetheless, somnolence, abnormal gait, and EPS were associated with risperidone treatment, and they appeared to be dose dependent. Also, abnormal gait, accidental injuries including falls, and somnolence were associated with olanzapine treatment in a dose range of 5, 10, or 15 mg daily.[21] In a recent double-blind trial conducted in patients with dementia comparing the efficacy of olanzapine versus placebo and risperidone, the frequency of treatment-emergent EPS and hyperprolactinemia was higher in the risperidone group relative to the olanzapine and placebo groups.[22]

In this study, risk estimates for olanzapine did not reach conventional levels of statistical significance. Residents were receiving olanzapine at a mean dose of 5 mg per day, which is lower than dosages reported in clinical trials and lower than that recommended by the Centers for Medicare and Medicaid Services guidelines for this population.[23] Moreover, the current study could have had limited power to detect any statistically significant effect associated with olanzapine due to the limited number of prescriptions (220 for olanzapine). Nonetheless, the excess risk associated with olanzapine could be clinically significant.

This study was underpowered to estimate the individual effect of other antipsychotic medications, including clozapine, quetiapine, and conventionals other than haloperidol. Due to their low prevalence, these agents have been included in the analysis grouped in the "other atypical" and "other conventional" categories. It is important to note that because we grouped together medications that differ substantially from each other, no inference can be drawn on the individual effect of agents, including clozapine, quetiapine, and conventionals other than haloperidol.

Antipsychotic medications may increase the risk of femur fracture through multiple mechanisms. The well-established risk of EPS associated with the use of conventional antipsychotics is believed to mediate the risk of fall and femur fracture. Evidence from clinical trials indicated a lower propensity of atypical agents to cause gait and movement disorders.[18–21] On the basis of this evidence, the use of atypical antipsychotics has been promoted, especially among elderly patients who may be particularly susceptible to develop antipsychotic-induced EPS. Nonetheless, there are data suggesting that the risk of developing EPS during treatment with atypical antipsychotics is clinically relevant and dose-dependent.[20] Also, a very recent study has shown that treatment with atypical and conventional antipsychotics is equally associated with an increased risk of EPS and tardive dyskinesia among older adults with dementia.[24] Atypical antipsychotics block D_2 receptors, but they also antagonize serotonergic, muscarinic, histaminergic, and α_1-adrenergic receptors, leading to a possible increased risk of confusion, delirium, excessive sedation, and orthostatic hypotension.[25] All of these are well-established etiologic factors for falls and related femur fractures. Finally, hyperprolactinemia associated with some of the atypicals—mostly risperidone—could be responsible for an accelerated loss of bone mineral density.[26]

This study provides results of clinical relevance, and it adds a piece of information to the public health debate on the use of atypical and conventional antipsychotics in the elderly population. Behavioral disturbances and psychosis represent a critical issue in geriatric medicine and public health. It has been shown that 15% of all residents in U.S. nursing homes receive antipsychotics, and most of them are prescribed an atypical agent.[27] Despite this widespread use, evidence supporting the efficacy and safety of atypical antipsychotics among patients with dementia is still limited.[28–30] Due to evidence from clinical trials suggesting a possible increased risk in death associated with atypical antipsychotics, the U.S. Food and Drug Administration has recently issued a warning to physicians pointing out the increased mortality and the fact that these drugs are not approved for this use.[31] The same agency is evaluating an extension of this warning to the use of conventional agents. In this study, we showed that both atypical and conventional antipsychotics may be related to an increased risk of femur fracture. This event represents a major public health issue as it may be associated with increased morbidity, risk of institutionalization, and mortality.[32] In times when physicians perceive a clinical benefit for patients treated with antipsychotics but need more efficacy and safety data to orient their clinical decision, information regarding the risk of fall or femur fracture associated with these medications is crucial.

This study has some limitations. Due to the lack of power and the low prevalence of antipsychotic use, clozapine, quetiapine, and conventionals other than haloperidol could not be analyzed individually. The use of claims data to ascertain the outcome introduces the potential for misclassification. By definition, we have missed all cases of femur fracture unrecognized or for which hospitalization was deemed unnecessary. However, this was probably a rare occurrence. Selection of controls is a critical issue in a case-control design. A reference group consisting of hospitalized controls appeared the most valid comparison group in our study. In fact, by doing so and by matching within facility, we have tried to control for patients' characteristics and other "forces" (structural and

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

organizational characteristics of the facility) influencing the probability of being hospitalized from a nursing home.[12] In a few cases, we had no information on whether the users were indeed taking antipsychotics at the time of hospitalization. This introduces a potential for misclassification of the exposure. With respect to dosages, we observed low variability among drug regimens, and we were not able to investigate dose-response relationships. Finally, although we controlled for numerous confounders, residual confounding is always possible.

In conclusion, this study has documented an increased risk of hospitalization for femur fracture associated with the use of conventional and some atypical antipsychotics among nursing home residents. Physicians should use these medications cautiously in the elderly population, especially among those patients presenting with a higher risk of falls.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

REFERENCES

1. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 2003;17:825–837
2. Hubbard R, Farrington P, Smith C, et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol 2003;158:77–84
3. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987;316:363–369
4. Wang PS, Bohn RL, Glynn RJ, et al. Zolpidem use and hip fractures in older people. J Am Geriatr Soc 2001;49:1685–1690
5. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, 1: psychotropic drugs. J Am Geriatr Soc 1999;47:30–39
6. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000;321:1371–1376
7. Glick ID, Murray SR, Vasudevan P, et al. Treatment with atypical antipsychotics: new indications and new populations. J Psychiatr Res 2001; 35:187–191
8. Hien le TT, Cumming RG, Cameron ID, et al. Atypical antipsychotic medications and risk of falls in residents of aged care facilities. J Am Geriatr Soc 2005;53:1290–1295
9. Bernabei R, Gambassi G, Lapane K, et al and the SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) Study Group. Characteristics of the SAGE database: a new resource for research on outcomes in long-term care. J Gerontol A Biol Sci Med Sci 1999;54: M25–M33
10. Gambassi G, Landi F, Peng L, et al. Validity of diagnostic and drug data in standardized nursing home assessments: potential for geriatric pharmacoepidemiology. Med Care 1998;36:167–179
11. World Health Organization. International Classification of Diseases, Ninth Revision (ICD-9). Geneva, Switzerland: World Health Organization; 1977
12. Intrator O, Castle NG, Mor V. Facility characteristics associated with hospitalization of nursing home residents: results of a national study. Med Care 1999;37:228–237
13. Rothman KJ, Greenland S, eds. Modern Epidemiology. 2nd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1998:96–105
14. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914–919
15. Morris JN, Fries BE, Mehr DR, et al. MDS Cognitive Performance Scale. J Gerontol 1994;49:M174–M182
16. Hartmaier SL, Sloane PD, Guess HA, et al. The MDS cognition scale: a valid instrument for identifying and staging nursing home residents using the Minimum Data Set. J Am Geriatr Soc 1994;42:1173–1180
17. Hosmer DW, Lemeshow S. Special topics: sample size issues when fitting logistic regression models. In: Applied Logistic Regression. 2nd ed. New York, NY: Wiley & Sons; 2000:339–347
18. Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134–143
19. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999;53:946–955
20. Katz IR, Jeste DV, Mintzer JE, et al and the Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60:107–115
21. Street JS, Clark WS, Gannon KS, et al, for the HGEU Study Group. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities: a double-blind, randomized, placebo controlled trial. Arch Gen Psychiatry 2000;57:968–976
22. Deberdt WG, Dysken MW, Rappaport SA, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry 2005;13:722–730
23. Gurvich T, Cunningham JA. Appropriate use of psychotropic drugs in nursing homes. Am Fam Physician 2000;61:1437–1446
24. Lee PE, Sykora K, Gill SS, et al. Antipsychotic medications and drug-induced movement disorders other than parkinsonism: a population-based cohort study in older adults. J Am Geriatr Soc 2005;53:1374–1379
25. Burns MJ. The pharmacology and toxicology of atypical antipsychotic agents. J Toxicol Clin Toxicol 2001;39:1–14
26. Becker D, Liver O, Mester R, et al. Risperidone, but not olanzapine, decreases bone mineral density in female premenopausal schizophrenia patients. J Clin Psychiatry 2003;64:761–766
27. Liperoti R, Mor V, Lapane KL, et al. The use of atypical antipsychotics in nursing homes. J Clin Psychiatry 2003;64:1106–1112
28. Lee PE, Gill SS, Freedman M, et al. Atypical antipsychotic drugs in the treatment of behavioral and psychological symptoms of dementia: systematic review. BMJ 2004;329:75–78
29. Liperoti R, Pedone C, Lapane KL, et al. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. Arch Intern Med 2005;165:2677–2682
30. Liperoti R, Gambassi G, Lapane KL, et al. Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. J Clin Psychiatry 2005;66:1090–1096
31. US Food and Drug Administration. FDA Public Health Advisory: Deaths with antipsychotics in elderly patients with behavioral disturbances. Available at: http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed April 11, 2005
32. Cree M, Soskolne CL, Belseck E, et al. Mortality and institutionalization following hip fracture. J Am Geriatr Soc 2000;48:283–288

 © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC © COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC