

ANTIDEPRESSANTS AND THE RISK OF FALLS AMONG NURSING HOME RESIDENTS

PURUSHOTTAM B. THAPA, M.B., B.S., M.P.H., PATRICIA GIDEON, R.N., TERRY W. COST, D.PH.,
AMANDA B. MILAM, PHARM.D., AND WAYNE A. RAY, PH.D.

ABSTRACT

Background In nursing home residents, the use of tricyclic and other heterocyclic antidepressants is associated with an increased risk of falls. The newer selective serotonin-reuptake-inhibitor antidepressants are largely free of the side effects of the tricyclic agents thought to cause falls and so have been hypothesized to be safer for those at high risk for falls.

Methods We retrospectively identified an inception cohort of 2428 nursing home residents in Tennessee who were new users of tricyclic antidepressants (665 subjects), selective serotonin-reuptake inhibitors (612 subjects), or trazodone (304 subjects) or nonusers of antidepressants (847 subjects). We ascertained the number of falls during therapy and during a similar follow-up period for nonusers, then calculated the rate ratios for falls with adjustments for an extensive set of potential confounding factors.

Results The new users of each type of antidepressant had higher rates of falls than the nonusers, with adjusted rate ratios of 2.0 (95 percent confidence interval, 1.8 to 2.2) for tricyclic antidepressants, 1.8 (1.6 to 2.0) for selective serotonin-reuptake inhibitors, and 1.2 (1.0 to 1.4) for trazodone. The rate ratios increased with the daily dose for tricyclic antidepressants, reaching 2.4 (95 percent confidence interval, 2.1 to 2.8) for doses of 50 mg or more of amitriptyline or its equivalent, and for the serotonin-reuptake inhibitors, reaching 1.9 (1.7 to 2.2) for 20 mg or more of fluoxetine or its equivalent. The elevated rates of falls persisted through the first 180 days of therapy and beyond.

Conclusions In this large study of nursing home residents, there was little difference in rates of falls between those treated with tricyclic antidepressants and those treated with selective serotonin-reuptake inhibitors. Hence, the preferential use of the newer antidepressants is unlikely to reduce the higher rate of falls among nursing home residents taking antidepressants. (N Engl J Med 1998;339:875-82.)

©1998, Massachusetts Medical Society.

MOOD disorders are common among nursing home residents^{1,2} and are associated with substantial excess morbidity and mortality.³⁻⁹ Although major depression is treatable in frail elderly persons,¹⁰ including nursing home residents,¹¹ there is concern that commonly used drugs increase the risk of falls and related injuries.^{12,13} Tricyclic and other heterocyclic antidepressants, until recently the predominant therapy among elderly patients, produce psychomotor impairment¹² and orthostasis,¹⁴⁻¹⁷ which can lead to

falls.^{13,18} In epidemiologic studies of long-term care, users of tricyclic antidepressants have increased rates of falls¹⁹⁻²² and injuries,²³⁻²⁵ with the increase in risk generally ranging from 50 percent to 200 percent. Because residents of long-term care facilities are very susceptible to falls and related injuries, with rates up to three times those of elderly persons living in the community,^{25,26} this possible adverse effect is of major concern.

Selective inhibitors of the reuptake of serotonin, effective antidepressants largely free of the adverse psychomotor and autonomic effects of tricyclic antidepressants,^{12,27} may be safer for frail elderly patients at high risk for falls.^{12,27} However, these drugs are expensive and have potentially undesirable effects in elderly patients.²⁷ We conducted a large inception-cohort study to compare directly the rate of falls among new users of tricyclic antidepressants with that among new users of selective serotonin-reuptake inhibitors.

METHODS

Cohort

Potential Members of the Cohort

We identified new users of tricyclic antidepressants, selective serotonin-reuptake inhibitors, or trazodone and residents who did not use any antidepressant in an inception-cohort design. We measured the risk factors for falls before the start of antidepressant therapy, because antidepressant drugs can affect these factors. The study included patients who terminated therapy early because of adverse effects of the medication that increased the risk of falls. The cohort was drawn from the computerized records of two pharmacy consultants in Tennessee that served a total of 80 nursing homes. We approached the 55 facilities with the most frequent use of selective serotonin-reuptake inhibitors, of which 54 agreed to participate and 53 had records of adequate quality. For each facility, we then designated a study period during which residents were eligible for inclusion in the cohort (the beginning of the period varied from 1993 to 1996, depending on when we contacted the facility and its retention of records). The length of the study period varied among the facilities.

New Users of Antidepressants

For each resident identified as a new user of antidepressants, we reviewed medication-administration and other records to confirm drug use and eligibility for the cohort. New users had to have been in the facility for 30 days or more (to be reliably identified by the consulting pharmacists' monthly records) and to have a qualifying

From the Division of Pharmacoepidemiology, Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville (P.B.T., P.G., W.A.R.); Cost Consulting, Nashville (T.W.C.); and Pharmaceutical Consulting Services, Murfreesboro, Tenn. (A.B.M.). Address reprint requests to Dr. Ray at the Department of Preventive Medicine, Medical Center North, A-1124, Vanderbilt University Medical Center, Nashville, TN 37232.

episode of antidepressant use, defined as use that began during the study period and in the facility by a resident at least 65 years of age with no antidepressant use during the previous 90 days. If there were multiple qualifying episodes, we included only the first.

The analysis in this study was restricted to new users of either tricyclic or other heterocyclic antidepressants, selective serotonin-reuptake inhibitors, or trazodone, an atypical antidepressant commonly used in long-term care because of its sedative properties.²⁷ The analysis excluded users of multiple types of antidepressants and those for whom the primary reason for starting therapy was somatic (migraine, peripheral neuropathy, or pain).

Nonuser Control Subjects

Nonuser control subjects were randomly selected from among the residents not taking antidepressants. For logistic efficiency, one nonuser was selected for every pair of new users of antidepressants (stratified according to facility and type of antidepressant). The nonusers were matched to the date of admission (± 2 years) and the index date (the date antidepressant therapy began) of a randomly selected member of the new-user pair. Nonusers had to meet the same criteria for cohort eligibility on the index date as the new users.

Follow-up Period

The follow-up period began on the day after the index date. The follow-up period for new users ended at the time they left the facility (because of discharge, death, transfer, or a hospital stay of more than 14 days) or at the time of cessation of antidepressant use for more than 14 days, whichever was earlier, and for nonusers it ended at the time they left the facility, at the time they started antidepressant use, or at the time the matched new user's follow-up ended. The last study day was considered to contribute one half person-day to the follow-up period. Days on which multiple types of antidepressants or nonstudy antidepressants were used were excluded.

Data Collection

Base-line variables for which information was abstracted from the nursing home records included the admission date, demographic characteristics, current height and weight, ambulatory status, functional status (as defined in the Minimum Data Set²⁸), medications and physical restraints used in the previous 7 days, falls in the previous 90 days, and the primary reason antidepressant therapy was started (classified as depression or depressive symptoms, behavioral symptoms of dementia, insomnia, or anxiety, or other or unknown). Insomnia, a symptom of depression, was classified separately because it is a common reason for the use of tricyclic antidepressants in elderly patients. Missing values (which never involved more than 2.5 percent of the subjects) were resolved by imputation, with the assumption that data were missing completely at random.

The use and dose of antidepressants, benzodiazepines, antipsychotic drugs, and other sedative or hypnotic agents were abstracted for each day of study follow-up. Doses were converted into equivalent units on the basis of recommendations for elderly patients.²⁹

Outcome

The primary study outcome was the number of falls during the follow-up period, ascertained from both nursing home incident reports and medical records.³⁰ Injurious falls²⁵ were those that caused medically treated injuries (fractures, joint dislocations or sprains, sutured lacerations, or head injuries with altered consciousness).

Statistical Analysis

Follow-up for the antidepressant users was classified according to the type of drug and the dose taken each day, and univariate rates of falls and rate ratios (with the nonuser control subjects as the reference group) were calculated. Poisson regression models were used to adjust rate ratios for both base-line characteristics of

the subjects (age, sex, race, time since admission to facility, body-mass index, ambulatory status, number of activities of daily living in which the resident was totally dependent on care providers, incontinence, cognitive impairment, use of physical restraints, previous falls, and use of anticonvulsant or antiparkinsonian drugs) and time-dependent factors (use of benzodiazepines, antipsychotic drugs, or other sedatives and the number of days since the index date [1 to 30, 31 to 90, 91 to 180, or ≥ 181 days]). To control for coexisting illnesses, we also fitted models with terms for base-line use of medications, including analgesics, antihypertensive drugs, other cardiovascular drugs, hypoglycemic drugs, antimicrobial drugs, antihistamines, bronchodilators, and oral corticosteroids. These terms did not materially affect the estimates, so they were not included in the final model. There was no evidence of overdispersion,³¹ which suggests that the Poisson assumption was satisfied. Alternative mixed-effects Poisson regression models that controlled for the inclusion in the analysis of multiple falls per resident and effects due to the facility had essentially identical findings.

All P values are two-sided. P values for comparisons of adjusted rate ratios were calculated from single-degree-of-freedom contrasts with Wald statistics. All regressions were performed with SAS Proc Genmod Software (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Characteristics of the Cohort

The cohort included 2428 elderly nursing home residents, of whom 665 were new users of tricyclic antidepressants, 612 were new users of selective serotonin-reuptake inhibitors, and 304 were new users of trazodone; 847 did not use any antidepressants. During the 1460 person-years of study follow-up, members of the cohort had 3524 falls (241 per 100 person-years) and 213 injurious falls (15 per 100 person-years).

The study cohort was frail and highly impaired (Table 1). The mean age was 82 years, 75 percent were women, 60 percent used a wheelchair or were chairbound or bedbound, 35 percent were incontinent, 22 percent had major cognitive impairment, 24 percent had been physically restrained in the previous seven days, and 26 percent and 20 percent, respectively, used benzodiazepines or antipsychotic drugs at base line. In the 90 days preceding the index date, the members of the cohort had a mean number of falls of 0.8.

The base-line characteristics of the cohort varied markedly with the use or nonuse of antidepressants (Table 1). As compared with the nonusers, the users of antidepressants had greater mobility, increased use of psychotropic and other types of drugs, and roughly twice as many falls in the previous 90 days, suggesting a greater base-line risk of falls.^{25,32-34} The users of antidepressants were less likely to be black, had been admitted more recently to the facility, and had a lower prevalence of major cognitive impairment. As compared with the users of tricyclic antidepressants, the users of selective serotonin-reuptake inhibitors had been admitted to the facility more recently, had a lower prevalence of major cognitive impairment, and had a lower frequency of physical restraint. The users of trazodone had been admitted

TABLE 1. BASE-LINE CHARACTERISTICS OF THE COHORT.

CHARACTERISTIC	NONUSERS (N=847)	USERS OF TRICYCLIC ANTIDEPRESSANTS (N=665)	USERS OF SELECTIVE SEROTONIN- REUPTAKE INHIBITORS (N=612)	USERS OF TRAZODONE (N=304)
Female sex (%)	75.9	75.2	74.0	73.0
Black race (%)	13.2	5.1	5.9	6.6
Mean age (yr)	83.0	82.1	82.1	82.2
Body-mass index*	22.9	22.6	23.0	22.4
Admitted in previous 90 days (%)	23.5	34.0	45.0	40.8
Ambulatory (%)	36.8	38.5	43.0	43.1
Wheelchair-bound (%)	30.5	36.4	34.5	31.9
Chairbound or bedbound (%)	32.7	25.1	22.5	25.0
Mean no. of activities of daily living in which resident was totally de- pendent	1.5	1.2	1.1	1.1
Incontinent bladder or bowel (%)	41.6	32.2	30.1	30.9
Major cognitive impairment (%)	29.2	18.6	12.3	25.0
Physical restraints used (%)†	23.5	24.8	19.3	29.6
Mean no. of drug classes for medical illness‡	2.9	3.1	3.1	3.1
Use of anticonvulsant drug (%)†	11.5	11.6	9.5	11.2
Use of antiparkinsonian drug (%)†	6.0	7.4	4.9	6.9
Use of benzodiazepine (%)†	15.9	29.0	28.4	46.4
Use of other sedative or hypnotic drug (%)†	10.2	12.9	11.6	18.1
Use of antipsychotic drug (%)†	16.6	22.0	18.5	28.0
Mean no. of falls in previous 90 days§	0.5	0.8	1.0	1.1

*The body-mass index is the weight in kilograms divided by the square of the height in meters.

†Use occurred within seven days before the index date.

‡Classes are analgesics, antihypertensive drugs, cardiovascular drugs, hypoglycemic drugs, anti-microbial drugs, antihistamines, bronchodilators, and oral corticosteroids.

§The number of falls has been standardized for residents living in a facility for less than 90 days.

more recently, had a greater prevalence of major cognitive impairment, and were more likely to have used psychotropic drugs than the users of tricyclic antidepressants.

The primary reason for starting antidepressant therapy differed according to the type of drug. Depression or the occurrence of depressive symptoms was the primary indication for 55 percent of the users of tricyclic antidepressants, 74 percent of those who used selective serotonin-reuptake inhibitors ($P<0.001$ for the comparison with tricyclic agents), and 34 percent of those who used trazodone ($P<0.001$ for the comparison with tricyclic agents); behavioral symptoms of dementia were the primary indication for 18 percent, 11 percent, and 23 percent, respectively; insomnia or anxiety for 16 percent, 3 percent ($P<0.001$), and 36 percent ($P<0.001$); and other or unknown indications for 10 percent, 11 percent, and 8 percent.

The antidepressant drugs were used at relatively low doses. By day 7 of therapy, the mean daily doses were 37 mg of amitriptyline or its equivalent for those using tricyclic agents, 16 mg of fluoxetine or its equiv-

alent for those using selective serotonin-reuptake inhibitors, and 53 mg of trazodone for those using that drug.

Rates of Falls According to Type of Antidepressant

The users of each of the three types of antidepressants had a higher rate of falls than the nonusers, even after adjustments were made for differences in potential confounding factors (Table 2). The rate was highest for the users of tricyclic antidepressants, who had an adjusted rate ratio of 2.0 (95 percent confidence interval, 1.8 to 2.2). This was significantly greater than the rate ratios of 1.8 (1.6 to 2.0, $P=0.001$) for the users of selective serotonin-reuptake inhibitors and 1.2 (1.0 to 1.4, $P<0.001$) for the users of trazodone. Within each group, there were no significant differences between the users of individual drugs. For injurious falls, the adjusted rate ratios were greater than 1.0 for the users of each of the three types of antidepressants — 1.3 (95 percent confidence interval, 0.9 to 1.9) for those using tricyclic antidepressants, 1.7 (1.2 to 2.5) for those using selective

TABLE 2. RATE OF FALLS ACCORDING TO TYPE OF ANTIDEPRESSANT AND SPECIFIC DRUG.*

DRUG	NO. OF PERSON-YR	NO. OF FALLS	RATE PER 100 PERSON-YR	RATE RATIO (95% CI)	ADJUSTED RATE RATIO (95% CI)†
None	494.7	646	131	1.0	1.0
Tricyclic antidepressant					
All‡	463.0	1426	308	2.4 (2.1–2.6)	2.0 (1.8–2.2)
Nortriptyline	169.7	501	295	2.3 (2.0–2.5)	2.0 (1.8–2.3)
Amitriptyline	143.6	415	289	2.2 (2.0–2.5)	1.9 (1.7–2.1)
Doxepin	76.5	241	315	2.4 (2.1–2.8)	2.0 (1.7–2.3)
Imipramine	49.7	168	338	2.6 (2.2–3.1)	2.2 (1.8–2.6)
Other§	21.3	87	409	3.1 (2.5–3.9)	2.4 (1.9–3.0)
Selective serotonin-reuptake inhibitor					
All§	326.8	1024	313	2.4 (2.2–2.6)	1.8 (1.6–2.0)
Paroxetine	162.9	491	301	2.3 (2.1–2.6)	1.7 (1.5–1.9)
Fluoxetine	94.6	297	314	2.4 (2.1–2.8)	1.8 (1.6–2.1)
Sertraline	69.1	236	342	2.6 (2.3–3.0)	1.8 (1.5–2.1)
Trazodone	175.5	428	244	1.9 (1.7–2.1)	1.2 (1.0–1.4)

*CI denotes confidence interval.

†The rate ratio was adjusted with the Poisson regression model for age, sex, race, time since admission to the facility and since the index date, body-mass index, ambulatory status, number of activities of daily living in which the resident was totally dependent on care providers, incontinence, cognitive impairment, use of physical restraints, previous falls, and use of anticonvulsants, antiparkinsonian drugs, benzodiazepines, antipsychotics, and other sedatives.

‡This category includes 2.2 person-years and 14 falls for persons receiving multiple tricyclic antidepressants.

§This category includes 0.2 person-year for persons receiving multiple selective serotonin-reuptake inhibitors.

serotonin-reuptake inhibitors, and 1.1 (0.7 to 1.8) for those using trazodone — but the confidence intervals for the tricyclic agents and trazodone included 1, and there were no statistically significant differences among the rate ratios.

For the users of tricyclic and selective serotonin-reuptake-inhibitor antidepressants, the rate of falls increased with increasing daily doses of the drug (Table 3). The adjusted rate ratio for the users of tricyclic agents as compared with the nonusers was 1.2 for those who used 10 mg or less of amitriptyline or its equivalent and 2.4 for those who used more than 50 mg ($P < 0.001$ by the test for linear trend). For the users of selective serotonin-reuptake inhibitors, the adjusted rate ratio was 1.5 for those who used less than 20 mg of fluoxetine or its equivalent and 1.9 for those who used 20 mg or more ($P < 0.001$). However, for the users of trazodone, those who used less than 50 mg had a higher rate of falls than those who used 50 mg or more.

The elevated rates of falls for users of antidepressants persisted over the course of therapy (Fig. 1). The residents who received tricyclic agents or selective serotonin-reuptake inhibitors for more than 180 days (as compared with nonusers with similar duration of follow-up) had adjusted rate ratios of 2.0 and 1.9, respectively; these rate ratios were not significantly different ($P > 0.05$) from those for the first 30 days of therapy (2.5 and 2.1, respectively). Within

each period, the rate ratios were highest for the users of tricyclic antidepressants and lowest for the users of trazodone.

The rate of falls varied according to the primary reason antidepressant therapy was started. For each type of antidepressant, the residents who began taking the drug for behavioral symptoms of dementia (adjusted rate ratios: users of tricyclic antidepressants, 2.4 [95 percent confidence interval, 2.1 to 2.7]; users of selective serotonin-reuptake inhibitors, 2.3 [2.0 to 2.7]; and users of trazodone, 1.4 [1.1 to 1.7]) had higher rates of falls than those who began therapy for depression or depressive symptoms (rate ratios of 1.8 [95 percent confidence interval, 1.6 to 2.0], 1.7 [1.6 to 1.9], and 1.1 [0.9 to 1.3], respectively; $P < 0.001$ for the users of tricyclic agents and selective serotonin-reuptake inhibitors; $P = 0.03$ for the users of trazodone). The residents who began taking antidepressant drugs for insomnia or anxiety had the following adjusted rate ratios for falls: 2.4 (95 percent confidence interval, 2.1 to 2.8) for the users of tricyclic agents, 1.8 (1.3 to 2.4) for the users of selective serotonin-reuptake inhibitors, and 1.2 (1.0 to 1.4) for the users of trazodone.

We assessed the effect of excluding potentially atypical residents from the cohort: those who were chairbound or bedbound, who started antidepressant therapy for insomnia or anxiety, or who were receiving very low doses of antidepressants. None of

TABLE 3. RATE OF FALLS ACCORDING TO DOSE OF ANTIDEPRESSANT.*

DRUG AND DAILY DOSE	NO. OF PERSON-YR	NO. OF FALLS	RATE PER 100 PERSON-YR	ADJUSTED RATE RATIO (95% CI)†
Tricyclic antidepressant				
≤10 mg	41.4	88	213	1.2 (1.0–1.5)
11–25 mg	154.2	498	323	2.0 (1.8–2.3)
26–50 mg	166.5	523	314	2.1 (1.8–2.3)
>50 mg	100.9	317	314	2.4 (2.1–2.8)
Selective serotonin-reuptake inhibitor				
<20 mg	115.8	311	269	1.5 (1.3–1.7)
≥20 mg	211.0	713	338	1.9 (1.7–2.2)
Trazodone				
<50 mg	33.6	89	265	1.5 (1.2–1.8)
≥50 mg	141.9	339	239	1.1 (1.0–1.3)

*The reference category is nonusers of antidepressants. For tricyclic antidepressants, the doses of nortriptyline, protriptyline, and trimipramine are expressed as amitriptyline equivalents, with 25 mg, 15 mg, and 75 mg, respectively, assumed to be equivalent to 50 mg of amitriptyline. For selective serotonin-reuptake inhibitors, the doses are expressed as fluoxetine equivalents, with 20 mg and 50 mg of paroxetine and sertraline, respectively, assumed to be equivalent to 20 mg of fluoxetine.

†The rate ratios were adjusted with the Poisson regression model for age, sex, race, time since admission to the facility and since the index date, body-mass index, ambulatory status, number of activities of daily living in which the resident was totally dependent on care providers, incontinence, cognitive impairment, use of physical restraints, previous falls, and use of anticonvulsants, antiparkinsonian drugs, benzodiazepines, antipsychotics, and other sedatives. CI denotes confidence interval.

these exclusions materially changed the primary findings (Table 4).

Because cardiovascular disease increases the severity of orthostasis caused by tricyclic antidepressants,³⁵ we assessed the rate of falls according to the baseline use of cardiovascular medications (Table 4). For the users of tricyclic antidepressants, the adjusted rate ratios were 1.8 for those taking no cardiovascular medications and 3.3 for those taking three or more medications ($P<0.001$). In contrast, there was no such trend for the users of selective serotonin-reuptake inhibitors. Thus, there was no significant difference between the adjusted rate ratio for the users of tricyclic agents and that for the users of selective serotonin-reuptake inhibitors taking no more than one cardiovascular medication; however, the users of tricyclic agents had a greater rate of falls if they took two ($P<0.001$) or three or more ($P<0.001$) cardiovascular medications. The rate of falls among the users of trazodone did not vary according to base-line use of cardiovascular medications.

DISCUSSION

Our primary objective was to compare the relative safety of tricyclic and selective serotonin-reuptake-inhibitor antidepressants with regard to falls, a critical end point for frail elderly patients. When the study

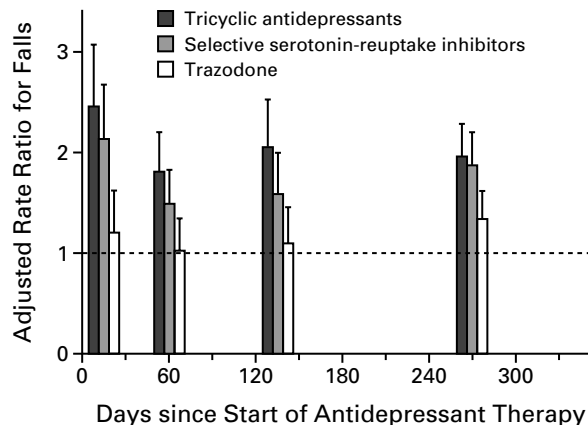


Figure 1. Adjusted Rate Ratios for Falls According to the Number of Days from the Start of Antidepressant Use.

The rate ratios were adjusted with the Poisson regression model for age, sex, race, time since admission to the facility and since the index date, body-mass index, ambulatory status, number of activities of daily living in which residents were totally dependent on care providers, incontinence, cognitive impairment, use of physical restraints, previous falls, and use of anticonvulsants, antiparkinsonian drugs, benzodiazepines, antipsychotics, and other sedatives. The data were plotted at the midpoint of the classification intervals of 1 to 30, 31 to 90, 91 to 180, and >180 days for the number of days since the index date. The reference category for all comparisons is nonusers of antidepressants with similar lengths of follow-up. For users of tricyclic antidepressants, selective serotonin-reuptake inhibitors, and trazodone and for nonusers, the respective numbers of person-years were as follows: 1 to 30 days since the index date, 48, 44, 22, and 62; 31 to 90 days, 79, 63, 31, and 94; 91 to 180 days, 92, 60, 34, and 100; and >180 days, 244, 160, 89, and 238. I bars indicate the upper bounds of the 95 percent confidence intervals. The dotted line represents a rate ratio of 1.0, or no difference from nonusers.

began, several reports had shown that older users of tricyclic antidepressants had increased rates of falls and related injuries,¹⁹⁻²⁵ which was consistent with the pharmacologic properties of such antidepressants and studies of surrogate end points.¹² However, this association was controversial³⁶ because these investigations had not been specifically designed to study antidepressants and consequently had small numbers of antidepressant users or limited measurement of potential confounding factors. The introduction and wide use of selective serotonin-reuptake inhibitors, which are largely free of the side effects thought to cause falls among the users of tricyclic antidepressants, provided the opportunity to address this clinical controversy by allowing a direct comparison of the rates of falls among the users of the two types of antidepressants.

The study was conducted among nursing home residents for several reasons. This population has a strikingly high prevalence of serious mood disorders, at least half of which are not treated.^{2,9} Because

TABLE 4. RATES OF FALLS WITHIN SUBGROUPS.

SUBGROUP	TRICYCLIC ANTIDEPRESSANT		SELECTIVE SEROTONIN-REUPTAKE INHIBITOR		TRAZODONE	
	NO. OF PERSON-YR	ADJUSTED RATE RATIO (95% CI)*	NO. OF PERSON-YR	ADJUSTED RATE RATIO (95% CI)*	NO. OF PERSON-YR	ADJUSTED RATE RATIO (95% CI)*
Mobile (by walking or wheelchair)†	350	2.0 (1.8–2.2)	254	1.7 (1.5–1.9)	146	1.0 (0.9–1.2)
Reason for starting antidepressant therapy not insomnia or anxiety‡	392	2.0 (1.8–2.2)	313	1.8 (1.6–2.0)	114	1.2 (1.0–1.4)
Not receiving very low dose of antidepressant§	422	2.1 (1.9–2.3)	325	1.8 (1.6–2.0)	175	1.2 (1.1–1.4)
No. of cardiovascular medications¶						
0	236	1.8 (1.6–2.0)	163	1.8 (1.6–2.0)	90	1.1 (0.9–1.3)
1	133	2.1 (1.7–2.5)	88	2.1 (1.7–2.5)	49	1.4 (1.1–1.9)
2	66	2.3 (1.8–2.9)	49	1.4 (1.1–1.8)	23	1.2 (0.9–1.7)
≥3	29	3.3 (2.3–4.8)	27	1.7 (1.2–2.5)	14	1.1 (0.7–2.0)

*The rate ratio was adjusted with the Poisson regression model for age, sex, race, time since admission to the facility and since the index date, body-mass index, ambulatory status, number of activities of daily living in which the resident was totally dependent on care providers, incontinence, cognitive impairment, use of physical restraints, previous falls, and use of anticonvulsants, antiparkinsonian drugs, benzodiazepines, antipsychotics, and other sedatives. CI denotes confidence interval.

†The reference category was nonusers of antidepressants who were mobile (either by walking or wheelchair) and who had 333 person-years of follow-up.

‡The reference category was nonusers of antidepressants who had 495 person-years of follow-up.

§A very low dose was defined as one equivalent to ≤10 mg of amitriptyline. The subgroup thus includes follow-up of subjects receiving doses of >10 mg of amitriptyline or its equivalent (tricyclic antidepressants), >5 mg of fluoxetine or its equivalent (selective serotonin-reuptake inhibitors), and ≥25 mg of trazodone. The reference category was nonusers of antidepressants with 495 person-years of follow-up.

¶Cardiovascular medications were antiarrhythmic drugs, anticoagulant drugs, digitalis glycosides, loop diuretics, and nitrates. The reference categories were nonusers of antidepressants who had 234, 138, 90, and 34 person-years of follow-up for 0, 1, 2, and ≥3 cardiovascular medications, respectively.

nursing home residents also have the greatest vulnerability to falls and related injuries,^{25,26} clarifying the relative potential of tricyclic and selective serotonin-reuptake-inhibitor antidepressants to cause falls is of major clinical importance. Nursing homes provided several logistic advantages that made it possible to study efficiently the large number of patients needed to detect differences between the drugs. First, nursing homes are federally required²⁸ to collect detailed information on the base-line risk factors for falls; second, records of medication administration track the type of antidepressants and the doses actually taken each day; and third, incident reports and other records provide a log of falls.

Our findings confirmed the association between the use of tricyclic antidepressants and increased rates of falls. After adjustments were made for potential confounding factors, the new users of these drugs had a rate of falls during therapy that was twice that of the nonusers of antidepressants. There was a pronounced dose-response relation, and the increased rate of falls persisted throughout the period of therapy. However, the new users of selective serotonin-

reuptake inhibitors also had a rate of falls that was 80 percent higher than that of the nonusers, and the rate increased with increasing dose and persisted throughout the period of therapy, although there was some evidence that these drugs were safer in the residents with more severe cardiovascular disease. Our findings are consistent with a recent report suggesting that both types of antidepressants confer an increased risk of hip fracture,³⁷ although that record-linkage study could not adjust for many potential confounding factors.

Our findings thus suggest either that the rate of falls is increased by the use of tricyclic or selective serotonin-reuptake-inhibitor antidepressants or that this increase is due to depression or its cofactors. Selective serotonin-reuptake inhibitors do not cause impairment as ascertained by most tests of psychomotor function and do not produce orthostasis and thus have not been thought to increase the risk of falls.¹² However, one study reported an increase in postural sway among older patients taking sertraline,³⁸ although this finding was not confirmed in subsequent reports on paroxetine, sertraline, and fluoxetine.^{39,40}

How could depression or its correlates increase the rate of falls? Because depression increases as the level of disability increases,⁴¹ we considered the possibility that our findings reflected base-line differences between the new users and the nonusers of antidepressant drugs. However, our findings persisted after we controlled for an extensive set of measures of base-line impairment, including functional status, cognitive impairment, medical illnesses, use of neurologic or psychotropic medications, and recent history of falls.

Our data are consistent with the hypothesis that a change in the health of residents of long-term care facilities that occurs near the time antidepressant therapy begins increases the rate of falls. This change could include the depression itself or worsening medical or neurologic conditions. A diagnostic hallmark of major depression is psychomotor impairment, and clinical experience suggests that depressed patients are "accident prone."^{42,43} Psychomotor impairment may be less responsive to therapy than neurovegetative and cognitive symptoms.^{44,45} Clinical experience suggests that in frail elderly patients, the onset or intensification of depressive symptoms often accompanies medical or neurologic deterioration.⁴¹ This line of reasoning is supported by the higher rates of falls among patients for whom behavioral symptoms — indicators of the progression of dementia — were the primary reasons for starting antidepressant therapy and by the persistence of increased rates of falls throughout the period of therapy.

The atypical antidepressant trazodone accounted for 18 percent of the antidepressant use by the cohort. Interestingly, the residents taking this drug had only a 20 percent increase in the rate of falls. Although trazodone is not thought to be a highly effective antidepressant,²⁷ it is strongly sedating and is thus commonly prescribed for agitation or insomnia.⁴⁶ Indeed, for 59 percent of the trazodone users, behavioral symptoms of dementia, insomnia, or anxiety were the primary reason for starting the drug. Thus, differences in the prevalence and severity of depression may have accounted for the lower rate of falls among the users of trazodone. This possibility is supported by the fact that the 20 percent increase in the rate of falls among the trazodone users was identical to that among the users of very low doses of tricyclic antidepressants (equivalent to 10 mg or less of amitriptyline), which, when given at these doses, have primarily hypnotic effects.⁴⁶

In summary, our findings suggest that the elevated rates of falls and related injuries among most nursing home residents taking tricyclic antidepressants would not be materially reduced by the preferential use of selective serotonin-reuptake inhibitors. All nursing home residents receiving antidepressants should be considered at increased risk for falls, and appropriate preventive countermeasures should be taken.⁴⁷

Supported in part by a grant from the Centers for Disease Control and Prevention (R49/CCR410144) and by a cooperative agreement with the Food and Drug Administration (FD-U-000073-11).

REFERENCES

1. Hyer L, Blazer DG. Depressive symptoms: impact and problems in long term care facilities. *Int J Behav Geriatr* 1982;1:33-45.
2. Parmelee PA, Katz IR, Lawton MP. Depression among institutionalized aged: assessment and prevalence estimation. *J Gerontol A Biol Sci Med Sci* 1989;44:M22-M29.
3. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA* 1989;262:914-9.
4. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA* 1990;264:2524-8.
5. Parmelee PA, Katz IR, Lawton MP. Depression and mortality among institutionalized aged. *J Gerontol* 1992;47:P3-P10.
6. Mossey JM, Mutran E, Knott K, Craik R. Determinants of recovery 12 months after hip fracture: the importance of psychosocial factors. *Am J Public Health* 1989;79:279-86.
7. Fredman L, Schoenbach VJ, Kaplan BH, et al. The association between depressive symptoms and mortality among older participants in the Epidemiologic Catchment Area-Piedmont Health Survey. *J Gerontol B Psychol Sci Soc Sci* 1989;44:S149-S156.
8. Murphy E, Smith R, Lindesay J, Slattery J. Increased mortality rates in late-life depression. *Br J Psychiatry* 1988;152:347-53.
9. Rovner BW, German PS, Brant LJ, Clark R, Burton L, Folstein MF. Depression and mortality in nursing homes. *JAMA* 1991;265:993-6. [Erratum, *JAMA* 1991;265:2672.]
10. NIH Consensus Development Panel on Depression in Late Life. Diagnosis and treatment of depression in late life. *JAMA* 1992;268:1018-24.
11. Katz IR, Simpson GM, Curlik SM, Parmelee PA, Muhly C. Pharmacologic treatment of major depression for elderly patients in residential care settings. *J Clin Psychiatry* 1990;51:Suppl:41-7.
12. Ray WA. Psychotropic drugs and injuries among the elderly: a review. *J Clin Psychopharmacol* 1992;12:386-96.
13. Monane M, Avorn J. Medications and falls: causation, correlation, and prevention. *Clin Geriatr Med* 1996;12:847-58.
14. Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants: a review. *Arch Gen Psychiatry* 1981;38:815-24.
15. Glassman AH, Bigger JT Jr, Giardina EV, Kantor SJ, Perel JM, Davies M. Clinical characteristics of imipramine-induced orthostatic hypotension. *Lancet* 1979;1:468-72.
16. Glassman AH, Walsh BT, Roose SP, et al. Factors related to orthostatic hypotension associated with tricyclic antidepressants. *J Clin Psychiatry* 1982;43:35-8.
17. Roose SP, Glassman AH, Giardina EGV, Walsh BT, Woodring S, Bigger JT. Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch Gen Psychiatry* 1987;44:273-5.
18. Thapa PB, Gideon P, Brockman KG, Fought RL, Ray WA. Clinical and biomechanical measures of balance as fall predictors in ambulatory nursing home residents. *J Gerontol A Biol Sci Med Sci* 1996;51:M239-M246.
19. Myers AH, Baker SP, Van Natta ML, Abbey H, Robinson EG. Risk factors associated with falls and injuries among elderly institutionalized persons. *Am J Epidemiol* 1991;133:1179-90.
20. Lipsitz LA, Jonsson PV, Kelley MM, Koestner JS. Causes and correlates of recurrent falls in ambulatory frail elderly. *J Gerontol A Biol Sci Med Sci* 1991;46:M114-M122.
21. Ruthazer R, Lipsitz LA. Antidepressants and falls among elderly people in long-term care. *Am J Public Health* 1993;83:746-9.
22. Thapa PB, Gideon P, Fought RL, Ray WA. Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents. *Am J Epidemiol* 1995;142:202-11.
23. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987;316:363-9.
24. Ray WA, Griffin MR, Malcolm E. Cyclic antidepressants and the risk of hip fracture. *Arch Intern Med* 1991;151:754-6.
25. Thapa PB, Brockman KG, Gideon P, Fought RL, Ray WA. Injurious falls in nonambulatory nursing home residents: a comparative study of circumstances, incidence, and risk factors. *J Am Geriatr Soc* 1996;44:273-8.
26. Tinetti ME, Speechley M. Prevention of falls among the elderly. *N Engl J Med* 1989;320:1055-9.
27. Small GW, Salzman C. Treatment of depression with new and atypical antidepressants. In: Salzman C, ed. *Clinical geriatric psychopharmacology*. 3rd ed. Baltimore: Williams & Wilkins, 1998:245-61.

28. Morris JN, Hawes C, Fries BE, et al. Designing the national resident assessment instrument for nursing homes. *Gerontologist* 1990;30:293-307.
29. Drug evaluations annual 1993. Chicago: American Medical Association, 1993.
30. Kanten DN, Mulrow CD, Gerety MB, Lichtenstein MJ, Aguilar C, Cornell JE. Falls: an examination of three reporting methods in nursing homes. *J Am Geriatr Soc* 1993;41:662-6.
31. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. New York: Chapman and Hall, 1989.
32. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med* 1986;80:429-34.
33. Tinetti ME, Liu WL, Ginter SF. Mechanical restraint use and fall-related injuries among residents of skilled nursing facilities. *Ann Intern Med* 1992;116:369-74.
34. Tideiksaar R. Falling in old age: its prevention and treatment in hospitals and nursing homes. New York: Springer Publishing, 1989.
35. Roose SP, Glassman AH, Giardina EGV, Johnson LL, Walsh BT, Bigger JT Jr. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J Clin Psychopharmacol* 1987;7:247-51.
36. Cumming RG, Nevitt MC, Cummings SR. Epidemiology of hip fractures. *Epidemiol Rev* 1997;19:244-57.
37. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors of tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 1998;351:1303-7.
38. Laghrissi-Thode F, Pollock BG, Miller M, Altieri L, Kupfer DJ. Comparative effects of sertraline and nortriptyline on body sway in older depressed patients. *Am J Geriatr Psychiatry* 1995;3:217-28.
39. Li X, Hamdy R, Sandborn W, Chi D, Dyer A. Long-term effects of antidepressants on balance, equilibrium, and postural reflexes. *Psychiatry Res* 1996;63:191-6.
40. Laghrissi-Thode F, Pollock BG, Miller MC, Mulsant BH, Altieri L, Finkel MS. Double-blind comparison of paroxetine and nortriptyline on the postural stability of late-life depressed patients. *Psychopharmacol Bull* 1995;31:659-63.
41. Katz IR, Miller D, Oslin D. Diagnosis of late-life depression. In: Salzman C, ed. *Clinical geriatric psychopharmacology*. 3rd ed. Baltimore: Williams & Wilkins, 1998:153-83.
42. Katz IR, Curlik S, Leshner EL. Use of antidepressants in the frail elderly: when, why, and how. *Clin Geriatr Med* 1988;4:203-22.
43. Seppälä T, Linnoila M, Mattila MJ. Psychomotor skills in depressed out-patients treated with L-tryptophan, doxepin, or chlorimipramine. *Ann Clin Res* 1978;10:214-21.
44. Sabbe B, van Hoof J, Hulstijn W, Zitman F. Changes in fine motor retardation in depressed patients treated with fluoxetine. *J Affect Disord* 1996;40:149-57.
45. Worthington J, Fava M, Davidson K, Alpert J, Nierenberg AA, Rosenbaum JF. Patterns of improvement in depressive symptoms with fluoxetine treatment. *Psychopharmacol Bull* 1995;31:223-6.
46. Reynolds CF III, Regestein Q, Nowell PD, Neylan TC. Treatment of insomnia in the elderly. In: Salzman C, ed. *Clinical geriatric psychopharmacology*. 3rd ed. Baltimore: Williams & Wilkins, 1998:395-416.
47. Ray WA, Taylor JA, Meador KG, et al. A randomized trial of a consultation service to reduce falls in nursing homes. *JAMA* 1997;278:557-62.