Risk Factors for Falls During Treatment of Late-Life Depression

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Background: Prior studies have found that antidepressant medications are associated with an increased risk of falling in elderly persons. However, little is known about the prevention of falls during treatment for depression in elderly persons. This study evaluated the time course and potential risk factors for falls in a treatment protocol for late-life depression to identify specific at-risk periods and risk factors for falls in this population.

Method: One hundred four subjects aged 69 years and over were treated in a protocolized manner using paroxetine and interpersonal psychotherapy. Those who did not respond received augmentation therapy with bupropion, nortriptyline, or lithium. Subjects were assessed at baseline and weekly during treatment; demographic and clinical characteristics of those who experienced a fall during treatment were compared with those who did not fall. Cox proportional hazards models were used to define risk factors for falls in univariate and multivariate models.

Results: During a mean of 21 weeks of treatment, 40 subjects (38%) fell. About half (53%) of the subjects fell during the first 6 weeks of treatment. In the multivariate model, memory impairment and orthostatic changes in blood pressure during treatment were risk factors for falling. Additionally, augmentation with bupropion appeared to be a risk factor for falls in univariate analysis, but this result is preliminary due to the small number of subjects who took bupropion.

Conclusion: Increased monitoring for falls is warranted during the acute treatment of late-life depression. When treating such patients, clinicians should be especially watchful of those with memory impairments or those who develop orthostatic blood pressure changes; orthostatic blood pressure should be measured throughout acute treatment. Additionally, augmenting paroxetine with bupropion may also increase the risk of falls, and this medication combination should be used with caution in elderly patients.

(J Clin Psychiatry 2002;63:936–941)

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Supported by grants K23 MH64196 (Dr. Lenze), P30 MH 52247, K02 MH01509, K05 MH00295, K01 MH01613, R37 MH43832, R01 MH37869, and T32 MH19986 from the National Institute of Mental Health, Rockville, Md.

Dr. Lenze has received grant/research support from Forest. Dr. Mulsant has been a consultant for, received honoraria from, and been a member of the speakers' or advisory boards of Eli Lilly, GlaxoSmithKline, and Pfizer; has received grant or research support from GlaxoSmithKline and Pfizer; and has provided expert testimony for GlaxoSmithKline. Dr. Reynolds has received grant/research support from GlaxoSmithKline and Forest. Dr. Pollock has been a consultant for GlaxoSmithKline, Organon, and Forest; has received grant/research support from Forest; and has received honoraria and been a member of the speakers' or advisory boards for GlaxoSmithKline, Forest, and Organon. Drs. Joo and Mazumdar and Mss. Begley, Weber, and Stack have no financial affiliation or other relationship to disclose relevant to the subject matter in this article.

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Falls are a serious public health problem in late life. They are the leading cause of injuries[1] and injury-related deaths among persons aged 65 and older.[2] They are the cause of about 95% of hip fractures in women[3]; hip fractures in turn are associated with decreased mobility, diminished quality of life, and premature death.[4] In particular, elderly persons receiving treatment for depression are at high risk for falls, as risk factors include age, cognitive impairment, disability, and white matter disease.[5–7] Also, depressive symptoms appear to be independently associated with increased risk of falls in elderly persons.[5,8] Further, the psychotropic medications commonly used in the treatment of late-life depression have been associated with increased risk of falls. For instance, sedatives (primarily benzodiazepines) have been reported to increase the fall risk by as much as 3.5-fold.[5] Other studies have reported that antidepressants (primarily tricyclic antidepressants [TCAs]) increase risk for falls.[9]

Controversy exists regarding the relative safety of newer antidepressants in regard to falls. Whereas TCAs are known to cause cognitive impairment and orthostatic hypotension, selective serotonin reuptake inhibitors (SSRIs) and other newer agents such as bupropion are

thought to be free of such effects. Pharmacoepidemiologic analyses have associated prescription both of TCAs and of SSRIs with an increased fall risk in elderly persons living in the community[10] and in nursing homes.[6] These studies and others[8] also suggest that depression itself may be a significant risk for falls, possibly confounding the observed association between falls and antidepressant treatment.

Although this literature suggests that elderly persons being treated for depression are at greatly increased risk of falls, it does not inform the clinician of the best way to monitor depressed elderly persons for fall risk during treatment. Further, although the treatment of depression often requires combinations of psychotropic medications, little is known about the risk of falls with commonly used combinations (such as 2 antidepressants, or an antidepressant plus a benzodiazepine). To better understand the association among falls, depression, and antidepressants, we examined data from a prospective study of elderly patients treated for depression. On the basis of previous literature, we hypothesized that more cognitively impaired and disabled subjects as well as those with orthostatic blood pressure changes would be at increased risk of falls. We also hypothesized that the use of multiple antidepressants or coprescription of benzodiazepines would increase the risk of falling. Finally, we examined the time course of falls to determine when during treatment subjects were most likely to fall; we hypothesized that falls were most likely to occur very early in acute treatment.

METHOD

This study examined data from the second Pittsburgh study of maintenance therapies in late-life depression (MTLD-2), a treatment study of pharmacotherapy and interpersonal psychotherapy for late-life depression.[11] This report is limited to the open-label acute and continuation phases of treatment. Subjects aged 69 years and older in an episode of single or recurrent major depressive disorder were assessed at baseline with a comprehensive battery that included the 17-item Hamilton Rating Scale for Depression (HAM-D),[12] the Mini-Mental State Examination (MMSE),[13] the Activities of Daily Living (ADL) scale,[14] the Mattis Dementia Rating Scale,[15] and the anxiety subscale of the Brief Symptom Inventory (BSI).[16] The study required subjects to have a baseline score of 15 or greater on the HAM-D and a score of 18 or greater on the MMSE. After written informed consent was obtained, a medical history was taken and the subjects were given a physical examination. From the results of the history and physical, total medical burden was quantified using the Cumulative Illness Rating Scale for Geriatrics.[17] During this examination, subjects were asked systematically about history of falls in the year prior to entry into the study, history of gait impairment, and history of lower extremity problems (e.g., arthritis). All subjects were ambulatory without supervision. Subjects were rated at each visit (including the termination visit if subjects dropped out for any reason) with the HAM-D and systematically asked at each visit whether they had fallen since their last visit. Also, changes in orthostatic blood pressure were assessed at baseline and at each visit.

During the acute phase of treatment, subjects were treated with paroxetine, starting at 10 mg/day and titrated as needed up to 40 mg/day, combined with weekly interpersonal psychotherapy (IPT) until they achieved remission of symptoms. Remission was defined as a score of 10 or less on the HAM-D for 3 consecutive weeks. After 8 weeks or longer, patients who did not fully respond to initial treatment received augmentation pharmacotherapy with bupropion (sustained release), nortriptyline, or lithium. Additionally, lorazepam, 0.5 to 2.0 mg/day, was used concurrently with antidepressant medication to relieve severe anxiety or insomnia. Subjects who remitted entered a 16-week continuation phase of open-label medication and IPT. During this time, subjects were seen biweekly. Those who completed this phase with HAM-D scores of 10 or less were defined as having recovered from their depressive episode and became eligible for the maintenance phase of the study (not included in the present analysis).

Statistical Analysis

For this analysis, subjects who reported at least 1 fall during acute or continuation treatment were designated as fallers. Baseline demographic and clinical characteristics were compared between those subjects who reported a fall and those who did not. To analyze the time course of falls, and to determine which variables were significant predictors of falling, we used univariate Cox proportional hazards models with time to first fall as the dependent variable.[18] Odd ratios (ORs) and 95% CIs for these ORs were determined. Prior to analyses, distributions of all variables were examined and a square root transformation was used to normalize the distribution of the BSI anxiety subscale. If subjects did not fall during acute or continuation treatment, they were treated as a censored observation. The Breslow method[19] was used to handle ties in failure time. Additionally, severity of depression as measured by HAM-D scores, orthostatic change in blood pressure, paroxetine dose, and use of bupropion and lorazepam (dummy coded: on/off) were examined as time-varying covariates (i.e., measures such as depressive symptoms or medication dose changed over the course of the study and so were measured in a time-dependent manner). Significant covariates ($p < .05$) from the univariate analyses were entered into a multivariate model to determine which variables were independently predictive of falling. Multivariate modeling was done using backward elimination to select the best explanatory variables. This method

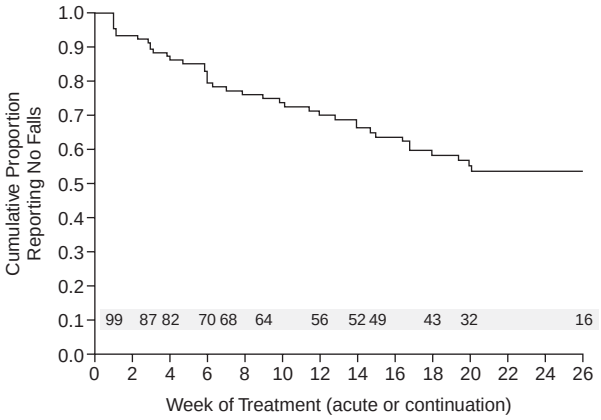
sequentially eliminates the least significant variables until only those meeting significance at the $p < .05$ level remain in the model.

RESULTS

The study group comprised 104 subjects, of whom 40 (38.5%) fell at least once during a mean of 21 weeks of treatment. Those who fell had a mean ± SD of 2.03 ± 1.37 falls (median = 1; range, 1–6). Figure 1 shows the cumulative time course for first falls during treatment. Fifty-three percent (21/40) of those who fell during the study had their first fall within 6 weeks of starting treatment. No subjects had a first fall after 21 weeks of treatment, although the size of the group was greatly decreased at that point (because subjects were censored from further analysis after they either dropped out, went on to maintenance treatment, or had already fallen). The 2 groups (those who fell and those who did not) were compared using baseline demographic and clinical measures shown in Table 1. In this univariate analysis, the variables significantly associated with falling were age, physical activities of daily living score, memory subscale score of the Mattis Dementia Rating Scale, and MMSE score.

We also examined several time-varying covariates (i.e., variables that changed over time such as medication doses and depressive symptom scores). In these univariate Cox models, we found that orthostatic change in blood pressure (lying-standing systolic measurement) was a significant predictor of falls (OR = 1.02, p = .018, 95% CI = 1.004 to 1.04). Paroxetine dose was not a significant predictor (OR = 1.03, p = .07, 95% CI = 0.998 to 1.06), nor was HAM-D score (OR = 1.04, p = .17, 95% CI = 0.98 to 1.10). We also evaluated bupropion use (i.e., the addition of bupropion to paroxetine to attain remission) as a time-varying covariate. Eighteen subjects were given augmentation therapy with bupropion, typically starting at 150 mg q.d. (lower dose if suggested by clinical judgment) and titrated (or reduced) as needed and tolerated to a mean ± SD final dose of 171 ± 81 mg/day (median = 150 mg; range, 100–300 mg). Of these, 5 fell while taking bupropion with paroxetine. Augmentation with bupropion was a significant time-varying covariate in the univariate Cox model (OR = 3.51, p = .01, 95% CI = 1.35 to 9.15). Because of the increased risk of falls associated with bupropion, which tended to be prescribed later in acute treatment (i.e., after a subject had not responded to a titration of paroxetine), we reevaluated the overall time course of falls with the survival analysis, censoring subjects when they were treated with bupropion. However, we did not find an appreciable change in the time course of falls with these subjects removed from the analysis, which continued to find that about one half of the falls occurred in the first 6 weeks of treatment (data not shown).

Figure 1. Time Course of Falls During Acute and Continuation Treatment in 104 Subjects (survival analysis)[a]



[a]Decreasing N (shaded) is due to censoring of subjects after they reported a fall, dropped out of treatment, or completed continuation treatment (i.e., recovered from depression).

We evaluated coprescription of lorazepam (used as an adjunct to help with sleep or anxiety) as a time-varying covariate. Forty-eight subjects received lorazepam, but this was not a significant covariate (OR = 1.29, p = .43, 95% CI = 0.68 to 2.46). None of the 9 subjects who were treated with nortriptyline fell and of the 7 subjects who took lithium, only 1 fell; therefore, no further analysis was done on these medications.

From the univariate analyses, 4 variables were entered into the multivariate analysis: age, physical ADL score, memory subscale score of the Mattis Dementia Rating Scale, and orthostatic blood pressure change (as a time-dependent covariate). MMSE score was not entered because this variable was highly correlated with the Mattis memory score, and bupropion augmentation was not added because only a small number of subjects received this medication. Table 2 shows the results of the multivariate analysis using backward elimination, revealing that only the Mattis memory score and orthostatic blood pressure change (as a time-dependent covariate) were significant predictors of fall risk. Because only a small number of subjects were augmented with bupropion, this variable was not added to the multivariate analysis.

Because we found that orthostatic pressure changes during treatment were a significant predictor of falls, we further evaluated group blood pressure changes in those who fell versus those who did not fall. We found no significant difference in the mean ± SD orthostatic systolic blood pressure drop between the 2 groups at baseline (subjects who fell, –8.4 ± 12.6 mm Hg vs. subjects who did not fall, –3.9 ± 14.9 mm Hg lying-standing blood pressure; t = –1.54, df = 102, p = .13). However, the group who fell did have a significantly greater mean orthostatic blood pressure drop in the measurement at the

Table 1. Baseline Demographic and Clinical Measures in Subjects Who Reported at Least 1 Fall (N = 40) Versus Those Who Reported No Falls (N = 64) During Acute and Continuation Treatment[a]

	No Falls			Fell				
Variable	N	%	Mean ± SD	N	%	Mean ± SD	Odds Ratio (95% CI)	p Value
Age, y[b]			76.2 ± 5.1			78.2 ± 5.9	1.06 (1.01 to 1.12)	.03
% Female	45	70.3	…	27	67.5	…	0.97 (0.50 to 1.88)	.92
% White	59	92.2	…	37	92.5	…	0.93 (0.29 to 3.02)	.90
% With ≥ 12 years of education	46/55	83.6	…	28/38	73.7	…	0.54 (0.26 to 1.11)	.10
% With recurrent MDD	27	42.9	…	13	32.5	…	0.71 (0.37 to 1.38)	.31
Cumulative Illness Rating Scale								
Total	…	…	9.8 ± 3.8	…	…	10.4 ± 3.5	1.03 (0.95 to 1.12)	.48
Count	…	…	5.7 ± 1.9	…	…	6.0 ± 1.7	1.07 (0.90 to 1.26)	.45
ADL								
Instrumental ADLs	63	…	11.8 ± 2.7	40	…	11.1 ± 3.4	0.92 (0.84 to 1.01)	.06
Physical ADLs	61	…	14.4 ± 1.7	40	…	13.8 ± 1.7	0.85 (0.73 to 0.99)	.04
HAM-D			20.0 ± 3.1			21.1 ± 4.2	1.08 (0.99 to 1.18)	.09
Brief Symptom Inventory-anxiety subscale[c]	60	…	1.1 ± 0.9	40	…	1.2 ± 0.9	1.12 (0.60 to 2.08)	.73
Mattis Dementia Rating Scale	63	…		38	…			
Total score			133.1 ± 8.4			130.7 ± 10.1	0.98 (0.95 to 1.01)	.14
Attention subscale			35.4 ± 1.3			35.2 ± 1.8	0.85 (0.69 to 1.05)	.12
Initiation subscale			34.1 ± 4.4			34.0 ± 4.1	0.99 (0.92 to 1.05)	.70
Construction subscale			5.8 ± 0.5			5.6 ± 1.1	0.87 (0.66 to 1.15)	.32
Conceptualization subscale			35.3 ± 2.6			35.2 ± 3.6	1.00 (0.90 to 1.11)	.97
Memory subscale			22.4 ± 2.8			20.8 ± 3.6	0.87 (0.80 to 0.95)	.002
Mini-Mental State Examination[d]	64	…	27.0 ± 2.7	37	…	25.8 ± 3.1	0.89 (0.81 to 0.99)	.03
Evidence from medical history and physical examination								
History of falls	24/61	39.3	…	18/39	46.2	…	1.26 (0.67 to 2.36)	.47
Balance/gait problems	16/61	26.2	…	13/39	33.3	…	1.55 (0.79 to 3.01)	.20
Lower extremity problems (eg, arthritis)	40/61	65.6	…	20/39	51.3	…	0.63 (0.34 to 1.18)	.15
Orthostatic BP change, mm Hg (systolic lying-standing)	…	…	–3.9 ± 14.9	…	…	–8.4 ± 12.6	1.01 (0.99 to 1.04)	.22

[a]Comparisons were made using univariate Cox proportional hazards models (time to first fall as dependent variable). Abbreviations: ADL scale = Activities of Daily Living scale, BP = blood pressure, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder.
[b]Age range: no falls = 69–88 years; fell = 70–93 years.
[c]SQRT(X) transformation used in analysis (original means and standard deviations reported).
[d]Score calculated using serial 7 test of attention/calculation.

end of acute treatment (fell, –6.8 ± 12.6 vs. did not fall, –1.1 ± 12.2; t = –2.28, df = 102, p = .025).

DISCUSSION

In this study of elderly persons treated with paroxetine and interpersonal psychotherapy for a major depressive episode, we found that falls were more likely to occur earlier in treatment (especially in the first 6 weeks). Patients were at increased risk for falls if they had memory impairment or orthostatic blood pressure changes during treatment. We also found that the augmentation strategy of adding bupropion to paroxetine may increase the risk of falls. Contrary to our hypothesis, coprescription of lorazepam was not found to be a risk factor for falls. Similarly, neither the dose of paroxetine nor augmentation with nortriptyline or lithium was associated with risk of falls.

Prior studies have found a consistent association between antidepressants and falls.[6] However, the published evidence is based solely on cross-sectional observational data, with minimal adjustment for confounds, dosage, or duration of therapy.[9] Our study differed in that it was a prospective study of a well-characterized ambulatory group receiving protocolized treatment for depression. This allowed us to examine treatment-related variables that increase the risk of falls. Our study has several potential limitations. The relatively small number of subjects taking a second antidepressant medication limited our ability to fully assess the risk-specific augmentation treatments. Also, as all patients were taking paroxetine by

Table 2. Multivariate Analysis of Baseline and Time-Varying Covariates as Risk Factors for Falls During Treatment[a] (N = 101: Fell = 38, No Fall = 63)

Variable	Chi-Square	p Value	Hazard Ratio (95% CI)
Mattis Dementia Rating Scale, memory subscale	7.68	.006	0.89 (0.81–0.97)
Orthostatic blood pressure changes[b]	4.25	.04	1.02 (1.001–1.041)

[a]Comparisons were made using a multivariate Cox proportional hazards model, with time to first fall as the dependent variable. A backward-stepping approach was used, with sequential elimination of the least significant variables until only those significant at the p < .05 level remained.
[b]The orthostatic blood pressure variable used in this analysis was the time-varying covariate (i.e., orthostatic changes during the course of treatment), not baseline (pretreatment) orthostatic changes.

study design, we could not determine the relative effect of paroxetine (versus a different antidepressant) on fall risk, although we could examine paroxetine dose-related effects. Notwithstanding these limitations, several of our findings deserve comment.

Our finding that falls tended to occur early in treatment is of import to clinicians involved in treating depressed elderly patients. This result is consistent with a previous study that found that new users of antidepressants were at a greater risk of falls compared to users who had been exposed to antidepressants for a longer period.[20] This greater risk may be due to a transient medication-induced postural instability; one study found that treatment with sertraline produced transient changes in body sway during the first week of treatment for late-life depression.[21] However, a similar study found no acute changes on body sway with paroxetine treatment,[22] and the mechanism for early treatment-related falls remains unclear. Another possible reason that falls may occur early in treatment is the effect of depression, which in itself is a risk factor for falls, possibly by inducing cognitive impairment.[23] However, we did not find that severity of depression at baseline or during treatment was a predictor of falling. In any event, this finding suggests that clinical vigilance and preventive measures should be taken early on when the risk of falling is greatest.

Consistent with previous studies, we found that orthostatic hypotension is an independent risk factor for falls. However, in our analysis, it was those orthostatic changes that occurred during treatment, rather than baseline (pretreatment) orthostasis, that were predictive of falls. For clinicians, this finding suggests that a baseline check of blood pressure is not a sufficient test for orthostasis; orthostatic blood pressures should be monitored throughout acute treatment. This monitoring should include systolic and diastolic blood pressure, as well as change in pulse from lying to standing, which can be sensitive to even mild orthostasis. Hypotensive patients should be identified and preventive measures instituted, such as hydration, improvement of lower extremity strength, and reduction or avoidance of medications that potentially can cause hypotension. Additionally, such patients should be instructed on how to stand up slowly and wait for 30 to 60 seconds before they start walking to decrease the risk of falling.

We found that subjects who received bupropion as augmentation therapy to paroxetine were at an increased risk for falls. The underlying mechanism is unknown; bupropion has not been reported to increase fall risk. However, on the basis of in vitro data, the potential for paroxetine to inhibit the cytochrome P450 2B6–mediated clearance of bupropion has been suggested.[24] Thus, subjects taking the combination of paroxetine and bupropion may have been at increased risk of falls due to high blood bupropion levels. Consistent with this hypothesis, we noted during the early part of the study that several subjects reported becoming acutely ataxic upon addition of bupropion to paroxetine. Once bupropion was discontinued, their subjective "drunk-feeling" and objective unsteadiness resolved. Later in the study, smaller doses of bupropion were used and these complaints became less frequent. Though this finding suggests that caution should be used when augmenting with bupropion, it must be considered preliminary due to the small number of subjects receiving these medications. However, the finding is quite relevant, as a survey of geriatric psychiatrists found that bupropion was the most popular augmentation agent with an SSRI in the treatment of late-life depression.[25]

Surprisingly, subjects were not found to be at increased risk of falls with the coprescription of lorazepam. It is possible that the low doses used in this study were less dangerous in terms of causing psychomotor impairments. Also, no subjects fell when treated with nortriptyline augmentation and only 1 subject fell when treated with lithium. The small number of subjects receiving either medication limits these results, although they do suggest that such augmentation strategies can be safe with respect to gait if medication levels are closely monitored.

In summary, the risk of falls is high during acute treatment of late-life depression. To decrease fall risk in their elderly patients, clinicians should assess cognitive impairment and should follow orthostatic blood pressure changes during treatment since these factors increase the risk of falling. Subjects at high risk of falling should be counseled on preventive measures. When augmentation therapy is necessary, caution should be taken when coprescribing bupropion with paroxetine. This vigilance is critical, especially early in treatment, as falls are a major source of preventable morbidity in elderly patients.

Drug names: bupropion (Wellbutrin and others), lorazepam (Ativan and others), nortriptyline (Aventyl and others), paroxetine (Paxil), sertraline (Zoloft).

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