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Non-tricyclic/non-selective serotonin reuptake inhibitor antidepressants and recurrent falls in frail older women

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Abstract

Objective—To determine the risk of recurrent falls associated with antidepressants other than tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs) among frail older women.

Design/data source—Secondary analysis of the Zoledronic acid in frail Elders to STrengthen bone (ZEST) trial data treated as a longitudinal cohort.

Residents/setting—181 frail, osteoporotic women 65 years old in long-term care.

Measurements—The primary exposure was individual non-TCA/non-SSRI antidepressants (i.e., serotonin norepinephrine reuptake inhibitors, mirtazapine, trazodone, and bupropion) at baseline and 6 months. The main outcome was recurrent (≥ 2) falls within 6 months after antidepressant exposure. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were derived using a generalized estimating equations model.

Results—At least 15% of women experienced recurrent falls between 0–6 or 6–12 months. At baseline and 6 months, 18.2% and 6.9% had a non-TCA/non-SSRI antidepressant, respectively. Adjusting for demographics, health status, and other drugs that increase risk of falls, non-TCA/non-SSRI antidepressant exposure significantly increased the risk of recurrent falls (AOR 2.14,

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95% CI 1.01–4.54). Fall risk further increased after removing bupropion from the non-TCA/non-SSRI antidepressant group in sensitivity analyses (AOR 2.73, CI 1.24–6.01).

Conclusions—Other antidepressant classes may not be safer than TCAs/SSRIs with respect to recurrent falls in frail older women.

Keywords

antidepressants; older adults; recurrent falls; long-term care; frailty

OBJECTIVE

According to a recent study from the Centers for Disease Control, 48% of all older long-term care residents have a diagnosis of depression (1). Also of note, various studies from the United States have documented that the prevalence of major depression in all older long-term care residents ranges between 4.8–24.6% (2,3). Despite the high prevalence of any and major depression, several studies suggest that long-term care residents with depression are undertreated, with 17–25% not receiving antidepressants (4, 5). Plausible explanations for underuse of antidepressants include utilization of non-pharmacological behavioral interventions and/or limited availability of geriatric psychiatry specialists in long-term care to guide diagnosis and treatment (1, 2, 4). Alternatively, low rates of prescribing may reflect hesitation stemming from limited data for antidepressant safety in older long-term care residents (6).

One major safety concern with the use of antidepressants is the risk of falls (7). Tricyclic antidepressants (TCAs) are known to increase the risk of falls (8–10). Additionally, the majority of published observational studies suggest selective serotonin reuptake inhibitors (SSRIs) also increase the risk of falls (8–11). Therefore, to avoid the risk of falls with TCA/SSRI antidepressants in older adults with depression, clinicians may select another antidepressant class, especially when other comorbidities (e.g., neuropathic pain, anxiety, or insomnia) exist (12).

To date, few studies have explored the relationship between non-TCA/non-SSRI antidepressants and falls in older adults (13, 14). Even fewer have focused on more clinically-relevant recurrent (i.e., ≥ 2) falls, a leading cause of hip fractures, hospitalization, and death (8, 15). Given this background, the aim of this study was determine the risk of recurrent falls associated with non-TCA/non-SSRI antidepressants among prefrail/frail older long-term care residents for whom multiple falls may be most concerning.

METHODS

Study Design/Data Source

Data for this cohort study were derived from the Zoledronic acid in frail Elders to STrengthen bone (ZEST) study, a double-blind, randomized controlled trial (ClinicalTrials.gov identifier: NCT00558012) (16). Complete study details appear elsewhere (16). Briefly, the sample included 181 frail women ≥ 65 years old in long-term care (e.g., nursing home or assisted-living). At baseline, 95% of participants were categorized as

prefrail or frail, with nearly three-quarters with dependency in 1 activity of daily living (16). Eligible participants were not receiving a bisphosphonate at the time of enrollment but had a history of osteoporosis or vertebral/hip fracture, a life expectancy of 2 years, and an estimated glomerular filtration rate of 30 mL/minute. All participants received calcium and vitamin D, while participants randomized to the intervention group also received a single infusion of zoledronic acid and were followed over 2 years. Information was collected regarding health status and functional abilities (16). Falls were captured by self-report, facility record review, and electronic medical record alert (16). Medication data (drug name, strength, dosage form, and frequency) were obtained from the medication administration record by trained research assistants at baseline and 6 months after study entry (16). Medications were coded using the Iowa Drug Identification System (17). The study was approved by the University of Pittsburgh Institutional Review Board and the Pennsylvania Department of Health. Informed consent was obtained for all participants.

Drug Exposure

The primary independent variables were exposure to individual/classes of antidepressants. Given their similar and well-established association with recurrent falls, as well as their inclusion in the 2015 American Geriatrics Society Beers criteria, TCAs (i.e., amitriptyline, imipramine, nortriptyline) and SSRIs (i.e., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) were categorized as *TCA/SSRI antidepressants* (8, 9, 18–20). *Non-TCA/non-SSRI antidepressants* included serotonin norepinephrine reuptake inhibitors (SNRIs, i.e., duloxetine, venlafaxine), mirtazapine, trazodone, and bupropion (21–23). It is important to note that all agents in the latter measure, with the exception of bupropion, increase serotonin. Specifically, SNRIs increase the concentrations of serotonin and norepinephrine by preventing reuptake into the presynaptic neuron (24). Similarly, trazodone inhibits serotonin reuptake, but also acts as an antagonist at the serotonin-2 receptor (24,25). Mirtazapine indirectly enhances serotonergic neurotransmission via blockade of alpha-2 auto- and heteroreceptors (24,26). Bupropion, however, is unique in that it affects dopamine and norepinephrine rather than serotonin (24). Therefore, in sensitivity analyses following a previously-published approach, non-TCA/non-SSRI antidepressants with high serotonergic activity (i.e., SNRIs, mirtazapine, and trazodone) were evaluated separately from bupropion, which has low serotonergic activity (23).

Outcome

The primary outcome was operationally defined as recurrent (i.e., 2) falls within 6 months after the last drug exposure assessment.

Covariates

Based on previously-published literature and clinical face validity, variables that may potentially confound the relationship between antidepressants and falls in long-term care residents were included (10). Demographics (i.e., age and race) were collected via enrollment documentation (16). For health status factors, cognition was measured using the Short Portable Mental Status Questionnaire (SPMSQ), where a lower score (range 0–10) indicates greater cognitive impairment and was included as a continuous covariate (27). History of fall in the previous year was collected by resident self-report. Medical conditions

were collected via participant self-report using a valid and reliable method to create a comorbidity index (28). We controlled for possible indications for antidepressants, including self-reported sleep problems, chronic pain, and diabetes mellitus (12). Additionally, a composite anxiety/depression variable was constructed using resident self-report (which included questions combining anxiety and depression symptoms) and the Patient Health Questionnaire (PHQ-9) depression scale, with a score ≥ 5 suggesting at least mild depressive symptoms (29). Other medications that may increase the risk of falls (i.e., antipsychotics, benzodiazepine receptor agonists, opioid receptor agonists that included tramadol, anticonvulsants) were also included as covariates (30, 31).

Statistical analysis

We computed univariate descriptive statistics to summarize participant characteristics at baseline, and exposure and outcome measures at each applicable time point. For the main analyses, we fitted a series of generalized estimating equations (GEE) models with recurrent falls in the period ensuing a drug exposure assessment as the dichotomous dependent variable; a binomial distribution and a logit link function for the dependent variable; any use of each of the individual drugs/classes of interest as the main independent variable; use of other antidepressants besides the one/class of interest as an essential covariate; and an exchangeable working correlation matrix to account for the contribution of potential multiple periods from the same participant (32).

We added time-varying covariates in the preceding paragraph as additional independent variables to control for potentially confounding factors. Odds ratios estimated from the GEE models, and their 95% confidence intervals and *p*-values obtained from the standard Wald *z*-test for the parameter estimates were used to draw main conclusions. Because there was a greater raw rate of falls in the active drug group of the ZEST Trial, we conducted a sensitivity analysis which included all independent variables from the final model as well as group status (received a bisphosphonate vs not). Also due to the lack of serotonergic activity of bupropion, we conducted sensitivity analyses excluding it from the non-TCA/non-SSRI composite variable. Finally, to address whether antidepressant discontinuation influenced our main findings, we restricted the analyses to the first six month period. All analyses were performed using SAS[®] software (version 9.3; SAS Institute Inc., Cary, NC).

RESULTS

All participants were females and were predominantly white, with a mean $\pm$ standard deviation age of 85.0 ± 5.1 years, 2.5 ± 1.1 comorbidity domains. Also at baseline, 72% were classified as intellectually intact, 14% as mildly cognitively impaired, 10% as moderately cognitively impaired and 4% as severely cognitively impaired. Depression/anxiety was the most common potential indication for antidepressants. The use of other medications that may increase falls ranged from 6.86 % for antipsychotics to 30.38% for opioid receptor agonists (Table 1) Antidepressant users compared to those taking none had more cognition test errors, and were more likely to have depression/anxiety and to take an opioid receptor agonist (Table 1).

At baseline, nearly 44% of participants were receiving at least one antidepressant, with more individuals taking TCA/SSRI antidepressants compared with non-TCA/non-SSRI antidepressants. Citalopram, escitalopram, and sertraline were the most common SSRIs. As seen in Table 2, among non-TCA/non-SSRI antidepressants, mirtazapine was the most common, followed by SNRIs, trazodone and bupropion. Use of all antidepressants/classes decreased at 6 months. During the first follow-up period (0–6 months), 18.2% of participants had at least 2 falls; this proportion decreased to 15.6% during the second follow-up interval (6–12 months).

Table 3 shows the results of the unadjusted and covariate-adjusted analyses for the primary and sensitivity analyses. In the primary analysis model, participants receiving TCA/SSRI antidepressants had a non-statistically significant increased risk of recurrent falls. Non-TCA/non-SSRI antidepressant use statistically significantly increased the risk of recurrent falls, even after controlling for demographics, health status, common indications for antidepressants, and other drugs that increase the risk of falls (AOR 2.14, 95% CI 1.01–4.54, $z = 1.99$, $p = 0.0468$). In the first sensitivity analysis controlling for group status (i.e., received bisphosphonate versus not), we found no meaningful differences in the adjusted odds ratios for TCA/SSRI antidepressant use or non-TCA/non-SSRI antidepressant use (AOR 1.48, CI 0.79–2.80, $z = 1.22$, $p = 0.2217$ and AOR 2.15, CI 0.97–4.76, $z = 1.89$, $p = 0.0583$, respectively). In an additional sensitivity analyses, removing bupropion from the non-TCA/non-SSRI antidepressant group further increased recurrent fall risk (AOR 2.73, CI 1.24–6.01, $z = 2.50$, $p = 0.0124$). No increased risk was immediately apparent with bupropion, though this finding was not statistically significant due to very few bupropion users (AOR 0.40, CI 0.06–2.59, $z = -0.96$, $p = 0.3382$). In the final sensitivity analysis restricted to the first 6 month period, no meaningful differences in the adjusted odds ratios for TCA/SSRI antidepressant use or non-TCA/non-SSRI antidepressant use (AOR 1.52, CI 0.62–3.77, $z = 0.91$, $p = 0.3628$ and AOR 2.92, CI 1.06–8.04, $z = 2.07$, $p = 0.0387$, respectively) were noted.

CONCLUSIONS

To the best of our knowledge, this is the first report to evaluate the risk of antidepressants other than TCAs and SSRIs on recurrent falls in prefrail/frail older long-term care residents. We found those exposed to non-TCA/non-SSRI antidepressants (i.e., SNRIs, mirtazapine, trazodone, bupropion) had a greater than two-fold increased risk of falls compared to older adults with no antidepressant exposure. These findings are robust to including group status as a covariate and restricting the analyses to the first 6 month period. These results are similar to findings from a recent cohort study by Coupland and colleagues that explored risks associated with different antidepressants/classes in more than 60,000 depressed older adults in general practices across the United Kingdom (21). Overall, those authors found non-TCA/non-SSRI antidepressants, including mirtazapine, trazodone, and venlafaxine, increased the risk of any fall by 39% (21). Two additional studies evaluated the relationship between antidepressants and hip fractures, which are likely due to a fall in older adults. The first by Gagne et al. using Medicare and prescription assistance program data for 10,844 propensity-matched, community-dwelling patients found a modestly increased rate of hip fracture (incident rate ratio 1.29, 95% CI 1.03–1.62) with non-TCA/non-SSRI

antidepressants (e.g., duloxetine, mirtazapine, trazodone) (22). The second study by Bakken and colleagues using Norwegian prescription claims and registry data for older adults not in long-term care found non-TCA/non-SSRI antidepressants (e.g., venlafaxine, duloxetine, mirtazapine, bupropion) were associated with an increased rate of hip fractures (standardized incidence ratio [SIR] 1.6, 95% CI 1.5–1.7) (23). The higher point estimates found in our study may reflect our focus on recurrent falls in prefrail/frail long-term care residents or, possibly, utilization of higher doses. In post hoc analyses, using previously-validated methods, we determined the standardized daily dose of the non-TCA/non-SSRI antidepressants by taking the resident's actual daily dose and dividing it by the geriatric minimum effective daily dose reported in a commonly-used pharmacotherapy textbook (31). On average, individuals in our study taking non-TCA/non-SSRI received doses that were 67–73% greater than the minimum effective geriatric dose for depression (30).

Interestingly, we did not find an increased risk of recurrent falls with bupropion. Removing bupropion from the non-TCA/non-SSRI antidepressant group increased the adjusted odds ratio for those drugs from 2.14 to 2.73, suggesting bupropion did not contribute to the increased risk of falls. One possible explanation is that the increased risk of falls may be due to modulation of the serotonergic system which is not affected by bupropion. Consistent with this hypothesis, Bakken et al. found antidepressants with high serotonergic activity were associated with a greater elevated risk than those with lower serotonergic activity, including bupropion (SIR 1.7, 95% CI 1.7–1.8 and SIR 1.2, 95% CI 1.1–1.5, respectively) (23). Beyond the lower risk for recurrent falls, bupropion has other attributes that may increase its appeal for use in elderly residents with depression. Unlike many other alternatives, the pharmacokinetics and efficacy of bupropion have specifically been studied in older adults and in individuals with comorbid cardiovascular disease (33–35). Bupropion may, however, lower the seizure threshold in those with epilepsy (20) and is a potent inhibitor of cytochrome 2D6 (36). Consequently, it should be used with caution in individuals receiving medications, such as certain opioids (e.g., hydrocodone), which are metabolized via this hepatic enzyme.

In addition to the cohort study design, a strength of our study was the use of multiple sources to ascertain falls, as opposed to just self-report that is commonly used in community-based studies. Additionally, medication ascertainment was from both the medical record and medication administration record, rather than pharmacy dispensing files. Moreover, we controlled for a number of potential confounders, including common indications for the use of antidepressants. Finally, this study included an often-neglected population which has a high prevalence of both depression and falls.

As with any study, however, some limitations should be noted. First, we did not have sufficient numbers of users for some individual medications/classes for robust analyses. However, we believe the odds ratios found represent the best approximation of the true magnitude of the association. Second, we were limited in our ability to test the impact of certain non-TCA/non-SSRI antidepressants, as they were either not prescribed (i.e., desvenlafaxine) or were not yet commercially available at the time of the ZEST trial (i.e., milnacipran). Thirdly, like all observational studies it is possible that the findings could have been affected by unmeasured confounders, and the limitation is not unique to our report.

However, we controlled for a number of known factors including common indications for antidepressant use. Finally, the ZEST trial enrolled predominantly prefrail and frail older women, which limits generalizability to men or more robust women.

Despite these potential limitations, the findings from our study suggest that with the exception of bupropion, non-TCA/non-SSRI antidepressants may not be safer than TCAs or SSRIs with regard to recurrent falls. Prescribers should be cognizant of such risks when prescribing SNRIs, mirtazapine, and trazodone to frail older adults, especially when they are explicitly selected because their adverse effect profile is perceived as less concerning. Further study is needed for more definitive findings with bupropion.

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Table 1

Baseline Characteristics of ZEST Study Sample (n=181)

Characteristic	No Antidepressant Use (n=102) n (%) or mean (SD) (n = 102)	Some Antidepressant Use (n=79) n (%) or mean (SD) (n=79)	P value
Age (years)	85.58 (4.64)	84.23 (5.59)	0.08
Black race	2 (1.96)	3 (3.79)	0.45
SMPSQ errors (0–10) *	1.46 (2.34)	2.35 (2.36)	0.01
History of fall in previous year	42 (41.18)	35 (44.30)	0.67
Modified comorbidity index (0–5 domains)	2.57 (1.13)	2.52 (1.12)	0.76
<i>Potential indications for antidepressants</i>			
Sleep problems	25 (24.51)	28 (35.44)	0.11
Chronic pain	14 (13.72)	14 (17.72)	0.46
Diabetes mellitus	21 (20.59)	14 (17.72)	0.62
Depression/anxiety	42 (41.17)	66 (83.54)	<0.01
<i>Other medications that increase risk of falls</i>			
Antipsychotics	7 (6.86)	10 (12.66)	0.18
Benzodiazepine receptor agonists †	18 (17.65)	20 (25.32)	0.20
Opioid receptor agonists ‡	18 (17.65)	24 (30.38)	0.04
Anticonvulsants	8 (7.84)	12 (15.19)	0.11

* Lower score indicates worse cognition; maximum score = 10.

† Includes benzodiazepines, zolpidem, zaleplon, eszopiclone.

‡ Includes tramadol.

Abbreviations: SMPSQ = Short Portable Mental Status Exam; ZEST = Zoledronic acid in frail Elders to Strengthen bone.

Table 2

Prevalence of Antidepressant Exposures over Time

Antidepressants/Classes	Baseline (n = 181) n (%)	6 months (n = 173) n (%)
TCAs	6 (3.3)	1 (0.6)
SSRIs	56 (30.9)	20 (11.6)
Any TCA/SSRI antidepressants	60 (33.1)	20 (11.6)
SNRIs	12 (6.6)	5 (2.9)
Mirtazapine	19 (10.5)	4 (2.3)
Trazodone	8 (4.4)	1 (0.6)
Bupropion	5 (2.8)	2 (1.2)
Any non-TCA/non- SSRI antidepressants	33 (18.2)	12 (6.9)

Abbreviations: SNRIs = serotonin norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

Table 3

Odds of Recurrent Falls with Antidepressants

Class	Unadjusted Odds Ratios (95% CI)	Adjusted* Odds Ratios (95% CI)
	z [p-Value]	z [p-Value]
<i>Primary analysis</i>		
TCA/SSRI antidepressants	1.50 (0.83, 2.71)	1.46 (0.78, 2.73)
	1.35 [0.1765]	1.17 [0.2421]
Non-TCA/non-SSRI antidepressants	2.22 (1.12, 4.39)	2.14 (1.01, 4.54)
	2.30 [0.0215]	1.99 [0.0468]
<i>1st Sensitivity analyses (adding group status)</i>		
TCA/SSRI antidepressants	1.56 (0.86–2.82)	1.48 (0.79, 2.80)
	1.47 [0.1426]	1.22 [0.2217]
Non-TCA/non-SSRI antidepressants	2.33 (1.15–4.74)	2.15 (0.97, 4.76)
	2.34 [0.0195]	1.89 [0.0583]
<i>2nd Sensitivity analyses (removing bupropion from non-TCA/non-SSRI antidepressants)</i>		
SNRIs and/or mirtazapine and/or trazodone	2.40 (1.17, 4.91)	2.73 (1.24, 6.01)
	2.40 [0.0164]	2.50 [0.0124]
Bupropion	0.71 (0.13, 3.87)	0.40 (0.06, 2.59)
	−0.40 [0.6903]	−0.96 [0.3382]
<i>3rd Sensitivity analyses (restricted to first 6 month period)</i>		
TCA/SSRI antidepressants	1.83 (0.84–4.04)	1.52 (0.62, 3.77)
	1.49 [0.1358]	0.91 [0.3628]
Non-TCA/non-SSRI antidepressants	2.87 (1.19–6.90)	2.92. (1.06, 8.04)
	2.35 [0.0188]	2.07 [0.0387]

* Adjusted for age, fall history, cognition, comorbidity index, sleep problems, chronic pain, diabetes, depression/anxiety, antipsychotics, benzodiazepine receptor agonists, opioids, anticonvulsants, other antidepressants; all covariates were time-varying.

Abbreviations: CI = confidence interval; SNRI = serotonin norepinephrine reuptake inhibitor. 95% CI = 95% Wald confidence interval for parameters of GEE model. z [p-Value] = Wald z-statistic and p-value for testing significance of parameter estimates from GEE models.