

# Number and Dosage of Central Nervous System Medications on Recurrent Falls in Community Elders: The Health, Aging and Body Composition Study

Joseph T. Hanlon,<sup>1,2,3</sup> Robert M. Boudreau,<sup>4</sup> Yazan F. Roumani,<sup>1</sup> Anne B. Newman,<sup>1,4</sup> Christine M. Ruby,<sup>2</sup> Rollin M. Wright,<sup>1</sup> Sarah N. Hilmer,<sup>5</sup> Ronald I. Shorr,<sup>6</sup> Douglas C. Bauer,<sup>7</sup> Eleanor M. Simonsick,<sup>8</sup> and Stephanie A. Studenski,<sup>1,3</sup> for the Health ABC study

<sup>1</sup>Department of Medicine (Geriatrics), School of Medicine and <sup>2</sup>Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pennsylvania.

<sup>3</sup>Center for Health Equity Research and Geriatric Research Education and Clinical Center, Veterans Affairs Pittsburgh Healthcare System, Pennsylvania.

<sup>4</sup>Department of Epidemiology, School of Public Health, University of Pittsburgh, Pennsylvania.

<sup>5</sup>Royal North Shore Hospital and University of Sydney, New South Wales, Australia.

<sup>6</sup>North Florida/South Georgia Veterans Health System Geriatric Research Education and Clinical Center, Gainesville, Florida.

<sup>7</sup>Division of General Internal Medicine, University of California at San Francisco.

<sup>8</sup>Intramural Research Program, National Institute on Aging, Baltimore, Maryland.

**Background.** Few studies have examined the risk of multiple or high doses of combined central nervous system (CNS) medication use for recurrent falls in the elderly. The study objective was to evaluate whether multiple- or high-dose CNS medication use in older adults was associated with a higher risk of recurrent ( $\geq 2$ ) falls.

**Methods.** This longitudinal cohort study included 3,055 participants from the Health, Aging and Body Composition study who were well functioning at baseline. CNS medication use (benzodiazepine and opioid receptor agonists, antipsychotics, antidepressants) was determined annually (except Year 4) during in-person interviews. The number and summed standard daily doses (SDDs; low, medium, and high) of CNS medications were computed. Falls 1 year later were ascertained annually for 5 years.

**Results.** For a period of 5 years, as many as 24.1% of CNS medication users took 2+ agents annually, whereas as no more than 18.9% of CNS medication users took high doses annually (3+ SDDs). Yearly, as many as 9.7% of participants reported recurrent falls. Multivariable Generalized Estimating Equation analyses showed that multiple CNS medication users compared with never users had an increased risk of sustaining 2+ falls (adjusted odds ratio [OR] 1.95; 95% confidence interval [CI] 1.35–2.81). Those taking high (3+) CNS SDDs also exhibited an increased risk of 2+ falls (adjusted OR 2.89; 95% CI 1.96–4.25).

**Conclusions.** Higher total daily doses of CNS medications were associated with recurrent falls. Further studies are needed to determine the impact of reducing the number of CNS medications and/or dosage on recurrent falls.

**Key Words:** Aged—Falls—Central nervous system medications.

FALLS commonly occur in community-dwelling elderly (1,2). A Health Aging and Body Composition (Health ABC) study found that at baseline, 24.1% of women and 18.3% of men reported falling in the previous year, of whom 30% had recurrent falls defined as two falls or more in the previous year (3). Recurrent falls may be more important to study than a single fall because multiple falls often signal a major problem and an increased risk for subsequent falls (1,2). Moreover, recurrent falls are associated with substantial morbidity and frequently lead elders to restrict their daily activity, leading to further mobility loss and balance problems (1,2).

Medications that affect the central nervous system (CNS), including both psychotropics and opioid analgesics, are among the most common classes of medications prescribed

for elders (4). The use of multiple CNS medications or CNS “polypharmacy” is also common in older adults (4,5). Previous studies have documented that elders taking a single medication from a specific CNS medication class (eg, benzodiazepines, antidepressants, antipsychotics, opioid analgesics) have an increased risk of single falls and fractures (6–8). Recently, a systematic examination of the relationship between the overall impact of medications from different classes that share similar pharmacological side effects on geriatric syndromes including falls has been recommended (8). To the best of our knowledge, only the study by Luukinen and colleagues (9) examined in community-dwelling elderly the risk of either of two CNS medications (ie, benzodiazepine and/or antidepressant) and recurrent falls. This study is limited by not addressing standardized

dosing of CNS medications (9). It is also important to note that these studies often did not control for a number of critical covariates including anticholinergics, or indications for the CNS medications. Given this background, the immediate objective of this study was to compare the association between the number and the dosage of CNS medications and recurrent falls.

## METHODS

### *Study Design, Setting, Source of Data, and Sample*

This cohort study included 3,075 Black and White men and women aged 70–79 years residing in specified zip code areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee, with no reported difficulty walking for ¼ mile, climbing 10 steps, or performing basic activities of daily living, enrolled between 1997 and 1998 in the Health ABC study and followed for 5 years (10). Twenty participants were excluded due to insufficient medication use information at baseline, leaving a sample of 3,055 participants included in the analysis. This study was approved by the University of Pittsburgh and University of Tennessee Memphis institutional review boards, and written informed consent was obtained from each participant prior to data collection.

### *Data Collection and Management*

The information collected over a 5-year period included a battery of detailed physiological and performance measurements and questionnaire material regarding sociodemographic characteristics, multiple aspects of health status, and medication use. For medications, at baseline (Year 1) and annually for 4 additional years except Year 4 (Years 2, 3, and 5), participants were asked to bring to clinic all prescription and over-the-counter medications they had taken in the previous 2 weeks. Well-trained examiners transcribed from the medication containers information on medication name; strength; dosage form; whether the medication was taken as needed; the number of times the respondent reported taking the product the previous day, week, or month; and when they started the medication. The medication data collected were coded using the Iowa Drug Information System codes and then entered into a computerized database (11). Data collected are considered highly accurate and complete and allow assessment of common confounders and outcomes (10,11).

### *CNS Medication Use Exposure*

The primary independent variable was use versus no use of CNS medications at baseline Year 1 and Years 2, 3, and 5. Therefore, CNS medication exposure always preceded the ascertainment of falls in the subsequent year. For example, Year 1 CNS drug use was a potential risk factor for falls

assessed at Year 2 and so on over the 6-year period. CNS medication use was derived from the above-mentioned computerized files of participants' coded prescription medication data. Consistent with previous work from our group, opioid receptor agonist analgesics, antidepressants, antipsychotics, and benzodiazepine receptor agonists comprised CNS medications (12). No one reported the use of a prescription non-benzodiazepine receptor agonist sedative hypnotic. Specifically, there was no use of the non-benzodiazepine sedative hypnotics (ie, ethchlorvynol, gluthethemide, chloral hydrate, amobarbital, pentobarbital, secobarbital).

We decided a priori to test the relationship between time-varying exposure to CNS medication dosage and recurrent falls. For current users of each regularly scheduled individual CNS medication at baseline and Years 2, 3, and 5, we calculated the average daily dose by multiplying the number of dosage forms taken the previous day by medication strength. The average daily dose was then converted to a summated standard daily dose (SDD) by dividing it by the minimum effective dose per day recommended for elders according to a well-respected geriatric pharmacotherapy reference (13). Thus, a person taking 1.0 standardized CNS medication unit will have taken the minimum recommended effective daily dose for elders for one agent (14). This procedure was performed for each CNS medication taken, and the individual CNS agent SDDs were summated to create an overall CNS standardized daily dosage. CNS standardized daily dosage was operationally defined based on the data distribution and clinical relevance into three categories: low dose (<1.0 SDD), medium dose ( $\geq 1.0$  to 3.0 SDD), and high dose (>3.0 SDD). A list of all specific medications included and their minimum effective daily dose is available upon request from the first author. We also operationally defined, based on the data distribution, time-varying independent categorical variables for the number of CNS medications used (1 or 2+). At baseline, duration of use was operationally defined as either "long term" (continuous use for previous 2 years) or "short term" (use only at the baseline in-person medication review). At follow-up Years 2, 3, and 5, duration of use among current users was operationally defined as either long term (use of any CNS medications at most recent and previous in-person medication reviews) or short term (use at most recent in-person medication review only). No CNS medication use was the reference group for all analyses.

### *Outcome Variables*

Participants were asked, "in the previous 12 months have you fallen and landed on the floor or ground." For those answering in the affirmative, they were asked, "how many times did you fall in the previous 12 months." The choices were one, two to three, four to five, six or more.

We operationally defined recurrent fallers as those participants who reported having fallen two or more times in

the previous year (2). Individuals who reported no or only one fall served as the comparison group (1–3). The fall variable was calculated using the 12 months prior to the time of the report (at Years 2, 3, 4, and 6) as the period of monitoring (3). Although this approach may lead to underreporting of falls due to recall bias, recall of falls for the preceding 12-month period is better than for a 3- or 6-month period (15). Moreover, recall of falls in the previous 12 months is highly specific (91%–95%) in comparison with that reported using more frequent prospective assessments (16).

### *Covariates*

We adjusted for potential confounding variables that may influence the relationship between CNS medication use and falls (1–3). Sociodemographic factors were represented by dichotomous variables for gender, site, living alone, and race. Race was self-reported as being either Black or White. Information about race was originally determined at baseline to assess its association with body composition. A continuous variable was created for age and a categorical variable for education (postsecondary education, high school graduate, and less than high school graduate). Health-related behaviors were characterized by categorical variables for baseline smoking (current, past, and never) and time-varying alcohol use (current, past, and never).

Health status factors were represented by dichotomous measures (present/absent) for self-reported health conditions including coronary heart disease, congestive heart failure, stroke, diabetes, hypertension, pulmonary disease, peripheral arterial disease, hearing impairment, and self-rated health (poor/fair vs good/excellent). Categorical variables were created for urinary problems (frequent leak, some, and never) and vision problems (excellent/good sight, fair sight, and poor to completely blind) (17). Measured weight and height were used to calculate body mass index (BMI) (weight [kg]/height [m<sup>2</sup>]), which was categorized as: under/normal (BMI <25.0), overweight (BMI: 25.0–29.9), and obese (BMI: 30.0 and above) (18). We also controlled for any use of cardiovascular medication classes known to be associated with falls and mobility (ie, diuretics, digoxin, Type IA antiarrhythmics) (19). In addition, we also controlled for time-varying dichotomous variable for anticholinergic medication use (defined as those agents with established muscarinic receptor affinity *in vitro* that also appear on a commonly accepted list of medications to be avoided in the elderly). This variable included antihistamines (eg, diphenhydramine) that are ingredients in over-the-counter sleep aids. We also created a continuous variable for polypharmacy represented by the number of prescription medications (excluding those mentioned above) being taken (20,21).

Possible indications for which CNS medications could be prescribed were also considered (22). Specifically, dichotomous measures were created (present/absent) for self-

reported sleep problems, anxiety, osteoarthritis, and cancer. A categorical variable was created for bodily pain (moderate or worse, mild, and none). Time-varying dichotomous measures were created for severe depressive symptoms (score >15 on Center for Epidemiologic Studies–Depression scale) and cognitive impairment (Modified Mini-Mental Status score <80) (23,24).

### *Statistical Analyses*

Categorical variables were summarized by percentages, and continuous variables were summarized by means (standard deviations) for all variables. A test of trend was conducted to examine the increase in CNS drug use over time. For the multivariable analyses, missing covariate values were replaced with those generated using the multiple imputation procedure in SAS software (SAS, Inc., Cary, NC). Multivariable Generalized Estimating Equation (GEE) analyses with an unstructured correlation matrix was used to model the correlated binomial outcome (ie, 2+ Falls: Yes/No) at Years 1, 2, 3, 4, and 6 (25–27). CNS medication use, anticholinergic use, alcohol use, depression, and cognitive impairment were entered as time-varying variables. All other variables were fixed. In separate models, odds ratios (ORs) and 95% confidence intervals and exact *p* values for each of the primary CNS medication use independent variables were computed-adjusted for all the covariates. We tested a two-way interaction between alcohol use and CNS medication use and recurrent falls. Tests for dose-response were performed by  $\chi^2$ -test for trend and multiple comparisons between multivariate adjusted ORs. Underlying statistical assumptions were evaluated and verified. All statistical analyses were conducted using SAS Version 9.1.

## **RESULTS**

The mean age was 74 years, and 51% were female (Table 1). The overwhelming majority reported excellent/good self-rated health and eyesight. One third reported having anxiety, and 8% reported sleep problems.

At baseline, 13.9% of participants used one or more CNS medications (Table 2). This rate increased over the course of the study to a high of 18.03% at Year 5 (test of trend; *p* < 0.001). The highest use of any individual class was 6.2% for antidepressant use. Few individuals (<1.5%) at any time point took three or more CNS agents. Nearly, 18% of current CNS medication users at baseline used high doses, whereas as many as 21.4% took two or more agents. Both types of CNS medication use increased over the course of the study. At baseline, more than half of the participants took a CNS drug for 2 or more years, which continued to increase over the following 4 years. By Year 5, 78.8% of participants taking high doses (3+ SDD) did so for 2 or more years.

A few examples of persons taking high doses at Year 5 include someone who was taking 8 mg of perphenazine daily, another one taking 100 mg of doxepin daily, and

Table 1. Characteristics of the Sample at Baseline ( $N = 3,055$ )

| Variables   | %     | Mean $\pm$ SD |
|---|-------|---------------|
| <b>Sociodemographics</b>  |       |               |
| Black race  | 41.44 |               |
| Female gender   | 51.52 |               |
| Age   |       | 74.00 (2.87)  |
| Site (Pittsburgh)   | 49.62 |               |
| <b>Education</b>  |       |               |
| Postsecondary   | 42.17 |               |
| High school graduate  | 32.69 |               |
| Less than high school graduate  | 25.14 |               |
| Living alone  | 30.21 |               |
| <b>Health-related behaviors</b>   |       |               |
| <b>Smoking status</b>   |       |               |
| Current   | 10.36 |               |
| Past  | 45.80 |               |
| Never   | 43.84 |               |
| <b>Alcohol use</b>  |       |               |
| Current   | 49.49 |               |
| Past  | 22.26 |               |
| Never   | 28.25 |               |
| <b>Health status</b>  |       |               |
| Coronary heart disease  | 17.06 |               |
| Congestive heart failure  | 1.33  |               |
| Stroke  | 2.36  |               |
| Diabetes  | 15.30 |               |
| Hypertension  | 44.63 |               |
| Pulmonary disease   | 4.17  |               |
| Peripheral arterial disease   | 5.31  |               |
| Hearing impairment  | 8.77  |               |
| Excellent/good self-rated health  | 83.84 |               |
| <b>Urinary problems</b>   |       |               |
| No leak   | 61.72 |               |
| Some leak   | 21.45 |               |
| Frequent leak   | 16.83 |               |
| <b>Vision problems</b>  |       |               |
| Excellent/good sight  | 79.35 |               |
| Fair sight  | 17.87 |               |
| Poor sight to completely blind  | 2.78  |               |
| <b>Body mass index</b>  |       |               |
| Underweight or normal   | 31.58 |               |
| Overweight  | 42.66 |               |
| Obese   | 25.76 |               |
| Diuretic use  | 25.76 |               |
| Digoxin use   | 6.78  |               |
| Type IA antiarrhythmic use  | 0.65  |               |
| Anticholinergic use*  | 12.73 |               |
| Polypharmacy (number of prescription medications excluding all the above and CNS medications) |       | 5.95 (4.00)   |
| <b>Possible indications for CNS medications</b>   |       |               |
| Sleep problems  | 8.13  |               |
| Anxiety   | 33.00 |               |
| Osteoarthritis  | 13.75 |               |
| Cancer  | 17.55 |               |
| <b>Bodily pain</b>  |       |               |
| None  | 33.68 |               |
| Mild pain   | 26.68 |               |
| Moderate pain or worse  | 39.64 |               |
| Severe depressive symptoms (CES-D >15)  | 4.75  |               |
| Cognitive impairment (Modified Mini-Mental Status <80)  | 10.00 |               |

Notes: CES-D = Center for Epidemiologic Studies–Depression scale; CNS = central nervous system.

\*A list of the 33 individual anticholinergic drugs is available upon request from the first author.

another taking both sertraline 100 mg daily and tramadol 200 mg daily.

At baseline, 6.1% of participants reported two or more falls in the previous year. Overall rates of falls were increasing in this elderly cohort to its highest point of 9.7% at Year 6. The GEE model estimates the ORs for falls relative to a referent (ie, no CNS use) rate of falls that was allowed to vary (increase) over time.

Table 3 shows the bivariable and multivariable relationship between recurrent falls and the number, dosage, and duration of CNS medication use in the previous year, adjusted for sociodemographic, health-related behaviors, health status factors, and indications for CNS medications. Both high-dose and multiple CNS medication use increased the risk of recurrent falls compared with no use. The increase in the adjusted OR with those taking three or more standardized doses was significantly ( $p < .05$ ) higher than those taking medium or low doses by direct comparison of the pairwise estimates. The interaction between alcohol and CNS medication use was not statistically significant ( $p > .05$ ). Both long and short duration of CNS medication use were associated with recurrent falls ( $p < .05$ ).

## DISCUSSION

This study examined time-varying CNS medication dosage of agents from any one of four therapeutic classes and found an increased risk of recurrent falls. There was a compelling dose–response relationship between total CNS medication dose and recurrent falls; those taking higher doses had a nearly threefold increased risk of recurrent falls. Because the OR for higher doses and recurrent falls was more than 2.0, the risk can be considered moderate to strong and is unlikely to be due to unmeasured confounding (6,22). These findings are also biologically plausible. Elders have an increased pharmacodynamic sensitivity to medications in each individual CNS medication class (ie, benzodiazepines, antidepressants, antipsychotics, and opioids), with increased sedation, dizziness, and increased postural sway (28,29). Moreover, use of medications in each individual CNS medication class has been shown to increase the risk of falls or fractures (10,30,31). Given this information, it is clinically sensible that combined doses of different medications that affect the CNS would indeed increase the risk of recurrent falls in elders.

Our findings are consistent with prior work on falls and multiple CNS medication classes. Elderly male outpatients taking two or more CNS medications (ie, benzodiazepines, other sedative/hypnotics, antidepressants, antipsychotics, and opioid analgesics) had a 2.37-fold increased risk of one or more falls that was assessed monthly by diary (12). This study did not examine recurrent falls and dose–response relationships and was limited to men. Elderly nursing home residents taking two or more psychotropics (ie, benzodiazepines, antipsychotics, antidepressants) or psychoactive

Table 2. Prevalence of CNS Medication Use and Dose Information Over Time\*

| CNS Medication Use        | Year 1 (N = 3,055), % | Year 2 (N = 2,911), % | Year 3 (N = 2,693), % | Year 5 (N = 2,480), % |
|---------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Use of 2+ agents          | 2.98                  | 3.85                  | 4.34                  | 4.29                  |
| Use of 1 agent            | 10.90                 | 10.55                 | 11.96                 | 13.74                 |
| High-dose use (>3 SDD)    | 2.39                  | 2.85                  | 3.04                  | 3.43                  |
| Medium-dose use (1–3 SDD) | 3.50                  | 4.19                  | 5.76                  | 6.33                  |
| Low-dose use (<1.0 SDD)   | 7.99                  | 7.46                  | 7.50                  | 8.27                  |
| Long-term use             | 7.79                  | 10.07                 | 11.33                 | 11.33                 |
| Short-term use            | 6.09                  | 4.43                  | 4.98                  | 6.69                  |

Notes: CNS = central nervous system; SDD = summated standard daily dose.

\*Test of trend using GENMOD in SAS;  $\chi^2 = 21.12$ ,  $df = 1$ ;  $p < .001$ .

agents (eg, opioids) had a 3.2- and 5.8-fold increased risk of one or more falls, respectively (32). This study did not examine recurrent falls, control for potential confounding, and dose–response relationships, and was limited to the nursing home setting. Finally, home-dwelling elderly taking either a benzodiazepine or an antidepressant had a 2.05-fold increase risk of two or more falls (9). This study did not examine other CNS active medications or dose–response relationships.

What are the clinical implications of these findings? First, clinicians should keep in mind that there is a cumulative effect or impact of using multiple medications that share a similar CNS adverse effect profile. Second, clinicians prescribing a high dose of an individual CNS medication or moderate doses of several CNS medications should carefully weigh the pros and cons of decreasing the dose or reducing the number of CNS agents. CNS medication reduction has been shown to reduce falls. In a double-blinded randomized controlled study by Campbell and colleagues (33), 93 elderly men and women currently taking a benzodiazepine, other hypnotic, or any antidepressant or antipsychotic, whose general practitioner thought might benefit from discontinuation, were randomly allocated to gradual withdrawal of psychotropic medication versus continued use. They found that patients assigned to the medication withdrawal group were 66% less likely to experience a fall during the 44-week follow-up (33). A more recent cohort study of 126 geriatric outpatients with one or more falls

examined withdrawal of one or more psychotropics in 29 of 33 patients (34). They found that those in medication withdrawal group were 44% less likely to experience a fall during the 12-week follow-up (34). In order to extend this work, additional studies should incorporate nonpharmacological methods to help participants tolerate the difficulties of CNS medication withdrawal (eg, insomnia, anxiety) and should include longer follow-up.

The current study has a number of strengths including the size and quality of data from this prospective cohort study. Also notable is that falls and medication use were monitored for 5 years, allowing for time-dependent analyses. The study carefully captured medication use using eyewitness recording of information from prescription medication labels and had exceptional rates of complete medication data capture (>99% of participants). This approach has been shown to be the most reliable method of determining medication information in community-dwelling elderly (35). We also used cutting-edge coding protocols for CNS medication categories and calculating cumulative doses. Previously, pharmacoepidemiological studies have used a valid measure promoted by the World Health Organization called “Defined Daily Dose” to categorize dosage (36). Although a defined daily dose is assumed to be the average maintenance dose per day for a medication used for its main indication in adults, its calculation is based on sales of medications per unit of population size and does not reflect actual prescribing patterns. Alternatively,

Table 3. Multivariable Relationship Between CNS Medication Use and Recurrent Falls\*

| CNS Medication Use          | Falls (2+ vs 0–1), Crude OR (95% CI) | Exact <i>p</i> Value | Falls (2+ vs 0–1), Adjusted OR (95% CI) | Exact <i>p</i> Value |
|-----------------------------|--------------------------------------|----------------------|---|----------------------|
| Use of 2+ agents            | 2.45 (1.71–3.51)                     | <.0001               | 1.95 (1.35–2.81)                        | .0004                |
| Use of 1 agent              | 1.79 (1.41–2.27)                     | <.0001               | 1.55 (1.22–1.97)                        | .0004                |
| No use                      | Reference                            |                      | Reference                               |                      |
| Higher dose use (>3 SDD)    | 3.47 (2.36–5.09)                     | <.0001               | 2.89 (1.96–4.25)                        | <.0001               |
| Moderate dose use (1–3 SDD) | 2.15 (1.58–2.94)                     | <.0001               | 1.80 (1.31–2.47)                        | .0003                |
| Lowest dose use (<1.0 SDD)  | 1.68 (1.12–2.49)                     | .01                  | 1.42 (0.95–2.15)                        | .5971                |
| No use                      | Reference                            |                      | Reference                               |                      |
| Long-term use               | 1.48 (1.24–1.77)                     | <.0001               | 1.76 (1.35–2.28)                        | <.0001               |
| Short-term use              | 1.36 (1.11–1.67)                     | <.001                | 1.49 (1.11–2.01)                        | .008                 |
| No use                      | Reference                            |                      | Reference                               |                      |

Notes: CI = confidence interval; CNS = central nervous system; OR = odds ratio; SDD = summated standard daily dose.

\*Multivariable Generalized Estimating Equation analyses adjusted for sociodemographic, health behavior, health status factors, and indications for CNS medications.

pharmacoepidemiological studies have calculated the daily doses of individual agents within a specific class of medications (eg, opioid analgesics) and converted them to a standard based on one specific medication within that class (eg, oral morphine equivalents) (37). This approach can work well if there are sufficient head-to-head studies of agents within an individual medication class to determine equivalent doses. Unfortunately, this approach does not work well when considering the common dosage across agents from multiple different therapeutic classes that share a common set of side effects (eg, CNS) especially in elders who are often underrepresented in clinical medication trials. We were able to summarize total dose exposure across agents in different classes by extending a previously validated approach for medications within an individual class (14,38).

There are several potential limitations to our study. Our query for falls is slightly different from the one recommended in 2005 by the Prevention of Falls Network Europe and Outcome Consensus Group, which is as follows: "Have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?" (39). Because our fall rates were derived from annual self-reports, the true rate may be underestimated compared with those ascertained by more frequent prospective monitoring (39). However, our rates of recurrent falls were similar to those in other studies. Moreover, the risk of CNS medications may be underestimated as medication use was measured at multiple fixed annual time points. In terms of other potential CNS active medications, we were not able to examine the impact of antiepileptic drugs because the rate of use was small (<3%), and we could not control for potential confounding by indication because the study did not ascertain the presence of common indications for antiepileptics such as epilepsy. Finally, this study of relatively well-functioning community-dwelling elders living in two U.S. states may not be representative of other populations elsewhere.

To conclude, these results suggest that the detrimental effects on recurrent falls are most pronounced in those taking higher CNS medication doses. Further studies are needed to determine the impact of reducing the number of CNS medications and/or dosage on recurrent falls.

#### FUNDING

This study was primarily supported by National Institute of Aging grants (R01AG027017; P30AG024827, N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106). This research was supported in part by the Intramural Research program of the National Institutes of Health, National Institute on Aging.

#### CONFLICT OF INTEREST

None reported.

#### ACKNOWLEDGMENTS

We acknowledge Darrell Abernethy, MD, PhD, and Donald E. Mager, PharmD, PhD, for the contributions in the design phase of this project. This study was presented in part at the Health ABC Study Symposium at the

Gerontological Society of America Annual Meeting, San Francisco, CA, November 2007.

#### CORRESPONDENCE

Address correspondence to Joseph T. Hanlon, PharmD, MS, Department of Medicine (Geriatrics), School of Medicine, University of Pittsburgh, Kaufman Medical Building, Suite 514, 3471 5th Avenue, Pittsburgh, PA 15213. Email: hanlonj@dom.pitt.edu

#### REFERENCES

- Hile ES, Studenski S. 2007. Instability and falls. *The Practice of Geriatrics*, 4th ed. E Duthie, P Katz and M Malone (eds). Philadelphia, PA: W.B. Saunders 195–218.
- Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med*. 1997;337:1279–1284.
- de Rekeneire N, Visser M, Peila R, et al. Is a fall just a fall: correlates of falling in healthy older persons. The Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2003;51:841–846.
- Hartikainen S, Mantyselka P, Louhivuori-Laako K, Enlund H, Sulkava R. Concomitant use of analgesics and psychotropics in home-dwelling elderly people-Kuopio 75 + study. *Br J Clin Pharmacol*. 2005;60:306–310.
- Hajjar E, Hanlon JT. 2006. Polypharmacy in the elderly. In *Geriatric Otolaryngology* (pp. 667–673), eds K Calhoun and DE Eibling. London, UK: Informa Healthcare.
- Hanlon JT, Cutson T, Ruby CM. Drug-related falls in the elderly. *Top Geriatr Rehabil*. 1996;11:38–54.
- Hartikainen SA, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol Med Sci*. 2007; 62A:MS1172–M1181.
- Agostini JV, Tinetti ME. Drugs and falls: rethinking the approach to medication risk in older adults. *J Am Geriatr Soc*. 2002;50: 1744–1745.
- Luukinen H, Koski K, Laippala P, Kivela SL. Predictors of falls among home dwelling elderly. *Scand J Prim Health Care*. 1995; 13:294–299.
- Newman AB, Haggerty CL, Kritchevsky SB, et al. Walking performance and cardiovascular response: associations with age and morbidity. The Health, Aging and Body Composition Study. *J Gerontol Med Sci*. 2003;58:M715–M720.
- Pahor M, Chrischilles EA, Guralnik JM, et al. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol*. 1994;10: 405–411.
- Weiner D, Hanlon JT, Studenski S. CNS drug-related falls liability in community dwelling elderly. *Gerontology*. 1998;44:217–221.
- Semla TP, Beizer JL, Higbee MD. 2007. *Geriatric Dosage Handbook*, 12th ed. Hudson, OH: Lexicomp.
- Hanlon JT, Horner RD, Schmader KE, et al. Benzodiazepine use and cognitive function among community dwelling elderly. *Clin Pharmacol Ther*. 1998;64:684–692.
- Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc*. 1988;36: 613–616.
- Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community dwelling older people: effect of the recall interval. *J Am Geriatr Soc*. 2005;53:2190–2194.
- Jackson RA, Vittinghoff E, Kanaya AM, et al. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. *Obstet Gynecol*. 2004;104:301–307.
- National Heart, Lung, and Blood Institute. 1998. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. [http://www.nhlbi.nih.gov/guidelines/obesity/ob\\_home.htm](http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm). Accessed October 17, 2007.
- Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc*. 1999;47:40–50.

20. Rudd KM, Raehl CL, Bond CA, Abbrusato TJ, Stenhouse AC. Methods for assessing drug-related anticholinergic activity. *Pharmacotherapy*. 2005;25:1592–1601.
21. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med*. 2003;163:2716–2724.
22. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc*. 1999;47:749–754.
23. Radloff LS. The CES-D scale: a self-report depression scale for research use in the general population. *Appl Psych Measur*. 1977;1:385–401.
24. Teng EL, Chui HC. The modified mini-mental state (3MS) examination. *J Clin Psych*. 1987;48:314–318.
25. Liang K, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22.
26. Diggle PJ. An approach to the analysis of repeated measures. *Biometrics*. 1988;44:959–971.
27. Diggle PJ, Heagerty P, Liang K, Zeger S (eds). 2002. *Analysis of Longitudinal Data*, 2nd ed. New York City, NY: Oxford University Press.
28. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2003;57:6–14.
29. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5(3):263–303.
30. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc*. 1999;47:30–39.
31. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Safety*. 2007;30:171–184.
32. Cooper JW, Freeman MH, Cook CL, Burfield AH. Assessment of psychotropic and psychoactive loads and falls in nursing facility residents. *Consult Pharm*. 2007;22:483–489.
33. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc*. 1999;47:850–853.
34. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol*. 2007;63:232–237.
35. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. *J Clin Epidemiol*. 1992;45:683–692.
36. Bergman U. The history of the Drug Utilization Research Group in Europe. *Pharmacoepidemiol Drug Safety*. 2006;15:95–98.
37. Hanlon JT, Guay DRP, Ives T. 2005. Oral analgesics: efficacy, mechanism of action, pharmacokinetics, adverse effects, drug interactions, and practical recommendations for use in older adults. *Pain in Older Persons, Progress in Pain Research and Management* Vol. 35 Gibson SJ Weiner DK (eds). Seattle, WA: IASP Press 205–222.
38. Reid LD, Johnson RE. Evaluation of the reliability and validity of a measure of anxiolytic drug use intensity for pharmacoepidemiologic studies. *Ann Pharmacother*. 1992;26:1441–1446.
39. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C on behalf of the Prevention of Falls Network Europe and Outcomes Consensus Group. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc*. 2005;53:1618–1622.

Received May 7, 2007

Accepted September 14, 2008

Decision Editor: Luigi Ferrucci, MD, PhD