Published in final edited form as:

Alzheimer Dis Assoc Disord. 2010 ; 24(1): 56–63. doi:10.1097/WAD.0b013e31819d6ec9.

Polypharmacy and Potentially Inappropriate Medication Use among Community-Dwelling Elders with Dementia

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Abstract

This cross-sectional study examines the association between total prescription medication use and potentially inappropriate medication use (PIRx) among community-dwelling elderly patients with and without dementia. Data (9/2005-9/2007) were from the NIA-funded National Alzheimer's Coordinating Center Uniform Data Set (UDS). The study analyzed the UDS initial visits of 4,518 community-dwelling subjects aged 65+ with and without dementia (2,665 and 1,853, respectively). PIRx was defined using a partial list of the 2003 Beers criteria. Generalized linear mixed models were applied to estimate the association between PIRx and polypharmacy. In both groups (with and without dementia), subjects who received PIRx on average took more medications than those taking no PIRx. As the total number of medications used increased, the odds of having PIRx also increased, controlling for dementia diagnosis and other subject characteristics. Our key findings were consistent after considering two definitions of PIRx (with or without oral estrogens) and accounting for missing data. In summary, the total number of medications used is associated with PIRx among ADC's community-dwelling elderly patients with and without dementia, with polypharmacy increasing the risk of PIRx. Ensuring appropriate medication use in this population is clinically important because of the significant risks for institutionalization.

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Keywords

prescription drugs; Beers criteria; Alzheimer's disease

Introduction

An objective of *Healthy People 2010* is ensuring safe and effective use of medical interventions among all older adults. Prescribing for elderly patients with dementia can be challenging because of the changing needs associated with cognitive decline and related behavioral and psychological symptoms.¹ In addition, more medications may be indicated among elderly patients with dementia for treatment of co-existing health conditions common in the aging population.² Although taking many prescription medications (i.e., polypharmacy) may be necessary for some individuals with complex illnesses, multiple medication use especially among elderly individuals can pose significant risk for medication error, non-adherence, and adverse drug-drug interactions.³ Epidemiological studies have found that taking a large number of prescription medications is associated with the use of unnecessary or inappropriate medications.⁴⁻⁶ Probably the most cited measure of potentially inappropriate medication use (PIRx), the Beers criteria contain medications that generally should be avoided among older adults because the health risks outweigh the benefits and because safer and/or more effective alternatives exist.^{7, 8} The Beers criteria identify a list of medications associated with increased adverse drug events and unnecessary hospitalization among elderly patients in ambulatory settings and nursing homes.⁹

Most studies on polypharmacy and PIRx have focused either on the general elderly population or on elderly patients with dementia living in residential care settings. Little is known, however, about prescription medication use in elderly persons with dementia residing in the community. Because many of these individuals with dementia are at the threshold of institutionalization, examining the quality of medication use in this population is particularly significant because both polypharmacy and PIRx may predispose them to conditions correlated with nursing home placement such as falls and behavioral symptoms.^{11, 12} Using data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), one of the most comprehensive tools currently available for investigating patients with dementia across the United States, the current study examines the total number of prescription medications used and its association with PIRx in community-dwelling elderly patients with and without dementia.

Methods

Data Source and Study Sample

This retrospective, cross-sectional study analyzed patients' initial visits captured with the UDS between 9/2005 and 9/2007. The UDS contains demographic and clinical data from patients with and without cognitive impairment enrolled in one of 29 Alzheimer's Disease Centers (ADCs) supported by the National Institute on Aging. Details about patient recruitment and assessment have been published elsewhere; thus only a brief summary is provided here.¹³ Since 2005, research-trained clinicians followed a uniform protocol to collect data from patients and their informants, typically a family member or close friend, during their ADC visits. Data reported by the patient or informant if present included, but were not limited to, patients' demographic characteristics (age, sex, race/ethnicity, education, marital status, and living arrangement); prescription medication use; cognitive status (severity of dementia according to the Clinical Dementia Rating [CDR] scale,¹⁴ and likely cause of dementia); functional status (the Functional Activities Questionnaire [FAQ])¹⁵ and general level of

dependence); behavioral assessment (the Neuropsychiatric Inventory-Questionnaire [NPI-Q] 16); and a pre-determined list of comorbid conditions.

The study sample included elderly individuals with and without dementia. To identify subjects with dementia, we first included 3,212 community-dwelling individuals aged 65 and older who did not meet “the standard criteria for dementia of the Alzheimer's type or for other non-Alzheimer's dementing disorders” as judged by a trained ADC clinician, and had CDR global scores ranging from 0.5 to 3.0 (very mild to severe dementia). Community-dwelling individuals were those living in an independent family residence or retirement community. Of the 3,212 individuals, we excluded the following 547 (17%) persons (not mutually exclusive): 415 with no reported data on prescription drug use, 118 with no accompanying informant present during their visit, and 85 with an informant deemed “unreliable” by ADCs' clinicians. The remaining 2,665 elderly patients with dementia were included into our study.

To identify subjects without dementia (control cases), we included 2,513 community-dwelling elders aged 65 and older who did not meet the standard criteria for dementia as judged by a trained ADC clinician, had CDR global score of 0 (no cognitive impairment), and had FAQ total score of 0 (no executive functional impairment related to cognition, such as the ability to shop, cook, and pay bills). Of these 2,513 individuals, we excluded the following 660 (26%): 641 with no reported prescription drug use and 19 with reported use of currently FDA-approved medications for treatment of Alzheimer's disease. In summary, the study sample that met the inclusion criteria included 4,518 subjects: 2,665 with dementia (59%) and 1,853 without dementia (41%).

Of the 4,518 study subjects, 4,087 (90%) had complete data: 2,467 subjects with dementia and 1,620 subjects without dementia. See Statistical Analysis section for discussion on sensitivity analysis of missing data. Approval from the Northwestern University's Institutional Review Board was obtained at the start of this study.

Measures

Total Number of Prescription Medications Used—The total number of prescription medications used was counted per patient for routinely scheduled medications (not “as-needed” or over-the-counter), excluding vitamins, herbal supplements, and topical agents. The variable was categorized as 1 to 2, 3 to 4, 5 to 6, 7 to 8, and 9 or more.

Potentially Inappropriate Medication Use (PIRx)—Beers 2003 criteria identified three types of PIRx: (1) medications that generally should be avoided among any elderly patients; (2) medications at a specified dose that should not be exceeded for any elderly patients; and (3) medications that should be avoided among certain elderly patients with specific comorbid conditions.⁸ Due to the nature of the data captured in the UDS, this study could not examine medications in the Beers criteria that had dosage specifications or that needed specific patient comorbid conditions. Therefore, PIRx was defined using a partial list of medications in the Beers 2003 criteria that included 44 agents/drug classes that should be avoided among all elderly patients regardless of health conditions, including dementia. Person-level dichotomous variables were constructed indicating whether PIRx occurred by matching the names and formulations of all medications taken by the subject with medications listed in the Beers criteria.

Subject Characteristics—Subject characteristics and their categorization are listed in Table 2. Age was calculated based on date of birth and date of initial visit. Race/ethnicity was combined into one variable based on separate questions regarding race and Hispanic/Latino origin. Level of dependence was assessed with a question asking whether the subject was able

to live independently, needed help with complex or basic activities of daily living, or was completely dependent on others.

Using the NPI-Q, we assessed the following eight neuropsychiatric symptoms: agitation, irritability, depression, anxiety, motor disturbance, disinhibition, delusions, and hallucinations. A factor analysis indicated that there were four factors with two symptoms clustered within each: (1) agitation and irritability, (2) depression and anxiety, (3) motor disturbance and disinhibition, and (4) delusions and hallucinations. Therefore, the eight neuropsychiatric symptoms were recategorized as the four factors (score range: 0 for no symptoms to 6 for severe in both symptoms) and each factor was analyzed accordingly in subsequent statistics analyses.

Dichotomous variables were created for seven health conditions based on co-existing diagnoses, procedures, and conditions captured in the UDS (“yes” if at least one was active or recent; “no” if otherwise): hypertension, hypercholesterolemia, incontinence (urinary or bowel), cardiovascular disease (heart attack, atrial fibrillation, angioplasty, cardiac bypass procedure, pacemaker, congestive heart failure, or other cardiovascular disease), thyroid disease, diabetes, and cerebrovascular disease (stroke, transient ischemic attack, or other cerebrovascular disease).

Severity of dementia was determined using the CDR global score, which summarized the degree of impairment in subjects' memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Although the Mini-Mental State Examination (MMSE) was available in the UDS, it was not used since it has been documented to yield potential false-positive scores among individuals with advanced age and high education.¹⁷ Likely cause of dementia was the primary diagnosis based on clinician assessment: probable and possible Alzheimer's disease, Lewy body dementia, frontotemporal dementia, Parkinson's disease, vascular dementia, primary progressive aphasia, and all others.

Statistical Analysis

Bivariate analyses (Pearson chi-square and Wilcoxon tests) examined the distributions of subject characteristics and total number of medications used according to dementia diagnosis and PIRx (among subjects with dementia, PIRx vs. no PIRx; among subjects without dementia, PIRx vs. no PIRx) when aggregated over each ADC. The significance levels were not adjusted for multiple comparisons, but the p-values from these tests were stratified by those attaining 0.05 and 0.001 significance levels which would correspond to performing 50 tests (Bonferroni adjustment, $0.05/50=0.001$). Generalized linear mixed effects models were applied to estimate the association between PIRx and total medication use, controlling for subject characteristics and ADC differences. To determine whether dementia diagnosis modified the relationship between total medication use and PIRx, an interaction between dementia diagnosis and total medication use was entered into the regression model.

Two secondary analyses were performed to further examine how robust the relationship between total medication use and PIRx was in different scenarios. First, preliminary analysis found that oral estrogens accounted for 22%, the highest proportion, of all PIRx cases and that the percentage of females with PIRx was disproportionately higher in subjects without dementia than in those with dementia (68% vs. 53%, $p<0.001$). We therefore performed a secondary analysis with a modified definition of “PIRx,” which excluded oral estrogens. Second, to determine the differential effect of the severity of dementia and the likely cause of dementia on PIRx, we performed a subset analysis by limiting the study sample to only patients with dementia.

Among the 4,518 study subjects who met the inclusion criteria, 431 (10%) had an item non-response in a subset of covariates of interest. The missing data were stratified into two mutually

exclusive subject groups, those missing a demographic/subject characteristic variable (n=97) and those missing all NPI-Q items (n=334). Subjects missing a demographic/subject characteristic variable were excluded from all analyses. The subjects without NPI-Q were excluded from the primary and secondary analyses (discussed above), but a best/worst case sensitivity analysis was performed to assess the impact of their exclusion. The analysis entailed repeating previous regression models by adding missing NPI-Q items with imputed values of extreme scores. All analyses were performed using R-version 2.7.0.¹⁸

Results

Bivariate Analysis

Table 1 shows the 4,087 subjects with complete data and their distribution of the total medication use, PIRx, and subject characteristics by dementia diagnosis and PIRx. (Additional data are available upon request.) Elderly subjects with dementia on average took more medications (mean=4.9; SD=2.6) than those without dementia (mean=3.9; SD=2.5; $p<0.001$). Among subjects with dementia, those taking at least one PIRx on average took more medications (mean=6.4; SD=2.8) than those taking no PIRx (mean=4.7; SD=2.5; $p<0.001$). Similarly, subjects without dementia taking at least one PIRx on average took more medications (mean = 5.0; SD=2.8) than those taking no PIRx (mean=3.6; SD=2.3; $p<0.001$).

Twenty percent (324/1,620) of elderly subjects without dementia compared to 15% (372/2,467) of those with dementia had at least one PIRx ($p<0.001$). The five most commonly used PIRx were similar between subjects with and without dementia: oral estrogens, muscle relaxants/antispasmodics, fluoxetine, short-acting nifedipine, and doxazosin. Of all PIRx cases, oral estrogens accounted for the highest proportion (22%) – substantially higher than muscle relaxants/antispasmodics (14%), fluoxetine (13%), short-acting nifedipine (11%), and doxazosin (7%). When PIRx was redefined without oral estrogens, the proportions of PIRx became similar between both groups (14% of subjects without dementia and 13% of subject with dementia; $p=0.60$).

Among subjects with dementia, more with PIRx were female, had lower education attainment, and had hypertension, incontinence, depression and anxiety than those without PIRx. Among elderly subjects without dementia, more with PIRx were female, had at most high school degree, and had incontinence than those without PIRx. The distribution of dementia severity is as follows: very mild dementia (16.7%), mild dementia (27.2%), moderate dementia (12.0%), and severe dementia (4.4%). The five most common likely causes of dementia were probable Alzheimer's disease (44.9%), possible Alzheimer's disease (5.6%), Lewy body dementia (2.9%), frontotemporal dementia (1.7%), and Parkinson's disease (1.2%).

Multivariate Analysis

Table 2 presents two multivariate generalized linear mixed models based on complete cases that display the associations between subject characteristics and two definitions of PIRx: Model A – PIRx with oral estrogens, and Model B – PIRx without oral estrogens. Model A indicates that as total medication use increased from “1 to 2” to “3 to 4,” the odds of having PIRx (with oral estrogens) also increased (OR= 2.85, 95% CI=2.12-3.83). The odds of having PIRx (with oral estrogens) continued to dramatically increase as total medication use increased, controlling for other subject characteristics. No significant interaction between dementia diagnosis and total medication use was observed; thus the interaction terms were excluded from the final model. Among the other subject characteristics, incontinence had significantly higher odds of having PIRx (with oral estrogens), while dementia diagnosis, male, hypercholesterolemia, cardiovascular disease, thyroid disease, and diabetes had lower odds.

Secondary and Sensitivity Analyses

Model B shows that as total medication use increased from “1 to 2” to “3 to 4,” the odds of having PIRx (without estrogen) also increased (OR=3.56, 95% CI=2.46-5.14). Similarly, the odds of having PIRx (without estrogen) continued to dramatically increase as total medication use increased. While the significance of gender disappeared when oral estrogens were removed from the definition of PIRx, the significance of the other subject characteristics remained the same in the two models.

Furthermore, a regression model was estimated using only subjects with dementia (Table 3). Both models showed that while the odds of having PIRx (with and without oral estrogens) increased as total medication use increased, Lewy body dementia had lower odds of having PIRx (with and without oral estrogens). In addition, controlling for other factors, the relationship between PIRx and severity of dementia was borderline statistically significant and inconsistent between the two models. In the sensitivity analysis, our findings from the complete cases were consistent with the best and worst case models.

Discussion

This study uses the UDS data collected at 29 ADCs across the US to examine total medication use and its relationship with PIRx among community-dwelling elderly subjects with and without dementia. Subjects with dementia generally have higher total prescription medication use than those without dementia. As the total number of medications used increases, the odds of having PIRx substantially increases, regardless of dementia diagnosis and other subject characteristics. Our findings did not change after considering two definitions of PIRx (with or without oral estrogens) and accounting for missing NPI-Q data. Furthermore, these findings do not vary significantly by dementia severity or likely cause of dementia. Consistent with prior studies,⁴⁻⁶ in which the estimated prevalence rate of PIRx as defined by Beers is about 20% in community-dwelling elders, our study provides further evidence that using many medications poses an elevated risk of PIRx.

Although taking many prescription medications may be necessary for some individuals, our findings raise important clinical concerns for elderly patients with dementia living in the community. More prudent care is warranted for this population because many of them are challenged by decreased decision-making capacity, problems with adhering to medications and reporting adverse effects, and unnecessary treatment burden for patients and their informal caregivers.¹⁹ Furthermore, because polypharmacy and PIRx may significantly increase the risk of falls and adverse drug effects, prescribing unnecessary or inappropriate medications in elderly patients with dementia may further contribute to their risks for conditions associated with nursing home admission. Clinical decision-making regarding prescription medications for elderly patients with dementia and with other co-existing health conditions need to balance the potential health benefits and risks in light of the patients' overall health profile, existing drug regimen, and preferences.²⁰

Examining the relationship between total medication use and other measures of prescription quality such as PIRx is important for understanding the appropriateness of taking many medications, especially among vulnerable older populations. Recent evidence, however, suggests that polypharmacy may not be a straightforward indicator of the quality of medication use. In a study of 196 outpatients aged 65 and older who were taking 5 or more medications, the incidences of both inappropriate use and underuse of medications were high, almost 65%.²¹ Patients taking between 5 and 8 medications were more likely to be missing a potentially beneficial drug than taking an inappropriate medication, suggesting that decreasing the number of medications alone may not effectively improve the quality of medication use. Further

investigation is needed to examine how generalizable those findings are to elderly patients with dementia.

Because we examined a partial list of the Beers medications, the prevalence of PIRx reported here is likely to be conservative. Furthermore, in the absence of detailed clinical information, defining PIRx using the Beers criteria in this study may lead to some misclassification of inappropriate medication use. Certain clinical situations in elderly patients with dementia may warrant a particular Beers medication. For example, patients with Lewy body dementia are often sensitive to neuroleptics, yet there are reports of good response to sub-therapeutic doses of antipsychotic medications when hallucinations and other behavioral problems are particularly problematic.²² Nonetheless, the Beers criteria have identified some medications that should be avoided if at all possible even among elderly patients with dementia. For example, patients with Alzheimer's disease are particularly sensitive to the cognitive impairments induced by drugs with anticholinergic properties, such as oxybutynin and tricyclic antidepressants.²³ Additional research may be necessary to examine more specific sets of medications-to-avoid for this population.

Since the publication of the Women's Health Initiative (WHI) study trial,²⁴ prescriptions for oral estrogens have decreased dramatically in the general elderly female population. Surprisingly, the present study found that the use of oral estrogens accounted for the majority of PIRx cases. According to the Beers 2003 criteria, oral estrogens can pose elevated risks of breast and endometrial cancer and had a lack of cardioprotective effect in older women.⁸ Moreover, estrogen use has been associated with greater cognitive decline in post-menopausal women compared to placebo.²⁵ With no preferred alternatives within the same drug class, prescribing decisions should be made based on the risk-benefit ratio for oral estrogens to the individual patient.

Many medications in the Beers criteria have common adverse effects including confusion, nightmares, agitation, and depression that are similar to neuropsychiatric symptoms often accompanying progressive neurodegeneration among dementia patients. For example, fluoxetine can greatly increase the risk of excessive CNS stimulation, sleep disturbances, and agitation.⁸ Muscle relaxants and antispasmodic agents can cause anticholinergic adverse effects and sedation. Elderly patients with dementia may be especially sensitive to these adverse drug effects because of physiological and metabolic changes associated with aging. Making sound clinical decisions may be challenging in this population even for experienced clinicians who need to distinguish adverse drug-induced effects from associated symptoms of dementia when prescribing medications.

Although not the focus, this study finds that the risk of PIRx varies by coexisting health conditions, after controlling for total medication use and other characteristics. In particular, incontinence was associated with an increased risk of PIRx perhaps because muscle relaxants/antispasmodics being the second most commonly used PIRx in the study sample are prescribed to treat incontinence. More research is needed to understand the mechanisms underlying these prescribing patterns.

There are additional limitations to this study. First, the UDS does not contain data from a randomized national sample of patients; therefore, the generalizability of these findings to all community-dwelling elderly patients with dementia will need to be further examined. Patient recruitment into ADCs may bias the UDS data toward more educated, higher income elders who received tertiary care from NIA-funded centers. This selection bias may also explain our finding that after controlling for total medication use, elderly patients with dementia had a lower risk of PIRx than those without dementia. It is possible that our findings may reflect better prescribing practices, besides total medication use, than those occurring in the

community. Second, despite having standardized protocol in data collection, the UDS relies on data entry at each ADC center that can lead to variation in data quality. Statistically, we have controlled for center effects to minimize potential bias in regression analyses. Third, because patients and proxy informants were asked to report patients' medication use, there is potential bias toward an underestimate of medication use. Fourth, because of the cross-sectional and non-experimental design of this study, causal relationships between polypharmacy and PIRx cannot be assumed. While it is possible that taking many medications may increase the risk of PIRx, having PIRx may also increase the risk of taking many medications because of potential adverse events that require medical treatment. Although not a limitation, caution should be used to interpret estimates because of the large sample in this study. Some of the statistically significant associations that were observed between patient characteristics and PIRx (e.g., age in Model A) may not be clinically meaningful.

In light of the significant risks for institutionalization among elderly patients with dementia, ensuring appropriate and safe medication use in this population is clinically important. This study provides additional evidence that a high volume of medication use (i.e., polypharmacy) is associated with elevated risks of PIRx among ADC's community-dwelling elderly patients with dementia. Prescribing physicians should continuously evaluate the necessity and appropriateness of all drug therapies prescribed according to best practices and patients' goals of care.

Acknowledgments

We thank Ms. Shanini Singh, a former volunteer at the Buehler Center on Aging, Health & Society, at Northwestern University, for her research assistance.

Dr. Lau was supported by a K-01 career development award (5K01AG027295-02) from the National Institute on Aging. Mr. Mercaldo was supported by the National Alzheimer's Coordinating Center under a research grant from the National Institute on Aging (U01AG016976). Dr. Trittschuh was supported by NIA training grant 1-T32AG20506-01-05, Mechanisms of Aging and Dementia (Disterhoft, PI). Dr. Shega was supported by a career development award sponsored by the National Palliative Care Research Center. Dr. Weintraub's role was supported in part by Alzheimer's Disease Core Center Grant AG13854 to Northwestern University (Mesulam, PI).

Funding Sources: None for the study. Dr. Lau was supported by a K-01 career development award (5K01AG027295-02) from the National Institute on Aging. Mr. Mercaldo was supported by the National Alzheimer's Coordinating Center under a research grant from the National Institute on Aging (U01AG016976). Dr. Trittschuh was supported by NIA training grant 1-T32AG20506-01-05, Mechanisms of Aging and Dementia (Disterhoft, PI). Dr. Shega was supported by a career development award sponsored by the National Palliative Care Research Center. Dr. Weintraub's role was supported in part by Alzheimer's Disease Core Center Grant AG13854 to Northwestern University (Mesulam, PI).

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Table 1
Subject Characteristics by Dementia Status and Potentially Inappropriate Medications Use (PIRx) Defined with Oral Estrogens

Subject Characteristics	Total Subjects ^a (N=4,087)	Subjects with Dementia (N=2,467)		Subjects without Dementia (N=1,620)	
		PIRx (N=372)	No PIRx ^b (N=2,095)	PIRx (N=324)	No PIRx ^c (N=1,296)
<u>Number of Medications Used</u>					
<i>Total Number (Mean ± SD)</i>	4.5 ±2.6	6.4±2.8	4.7 ±2.5**	5.0±2.8	3.6 ±2.3**
One to two (%)	24.5	4.3	19.6**	18.2	39.8**
Three to four	31.1	22.9	32.2	31.8	31.6
Five to six	24.3	30.4	27.9	23.5	17.0
Seven to Eight	12.2	23.4	12.5	15.4	7.8
Nine or more	7.8	19.1	7.8	11.1	3.9
<u>Socio-Demographic Characteristics</u>					
<i>Age (Mean ± SD)</i>	77.1 ±7.0	77.7 ±6.9	77.8 ±6.8	76.0 ±6.7	76.0 ±7.1
<i>Sex (%)</i> Female	59.0	60.0	52.0 *	77.0	65.0**
Male	41.0	40.0	48.0	23.0	35.0
<i>Race/Ethnicity (%)</i> White (non-Hispanic)	80.1	74.2	77.2	88.0	87.0
Black (non-Hispanic)	12.2	16.1	13.8	8.6	9.4
Hispanic	5.3	7.0	7.2	2.2	2.6
Others (non-Hispanic)	1.6	2.7	1.9	1.2	0.9
<i>Education level (%)</i> No high school degree	6.7	11.3	9.7*	0.3	2.0*
High school degree	27.6	38.7	32.6	22.8	17.3
College degree	40.2	31.2	37.7	45.1	45.7
Graduate degree	25.6	18.8	19.9	31.8	35.0
<i>Marital status (%)</i> Married or living as married	64.0	63.7	67.9	57.1	59.5
Widowed, divorced, or separated	32.9	33.1	30.4	38.9	35.4
Never married or Other	3.1	3.2	1.6	4.0	5.1
<i>Living Arrangement (%)</i> Alone	23.5	15.6	14.6	40.1	36.0
With spouse or partner	62.5	62.4	66.4	55.3	58.1
With other relatives or friends	12.2	19.9	16.3	4.3	5.3

Subject Characteristics	Total Subjects ^a (N=4,087)	Subjects with Dementia (N=2,467)		Subjects without Dementia (N=1,620)	
		PIRx (N=372)	No PIRx ^b (N=2,095)	PIRx (N=324)	No PIRx ^c (N=1,296)
With others	1.8	2.1	2.6	0.3	0.7
Level of Dependence (%) Able to live independently	49.8	17.5	18.1	98.2	98.4
Need help with complex activities	28.9	45.7	47.5	1.5	0.9
Need help with basic activities	15.7	27.7	25.2	0.3	0.8
Completely dependent	5.5	9.1	9.2	0.0	0.0
<u>Neuropsychiatric Symptoms (Score Range: 0-6)^d</u>					
Agitation and Irritability (Mean ± SD)	0.7 ± 1.3	1.3 ± 1.5	1.1 ± 1.4	0.1 ± 0.4	0.1 ± 0.5
Depression and Anxiety (Mean ± SD)	0.7 ± 1.2	1.2 ± 1.4	1.0 ± 1.3 [*]	0.2 ± 0.5	0.2 ± 0.6
Motor Disturbance and Disinhibition (Mean ± SD)	0.4 ± 1.0	0.7 ± 1.2	0.7 ± 1.2	0.0 ± 0.3	0.0 ± 0.2
Delusions and Hallucinations (Mean ± SD)	0.3 ± 0.8	0.5 ± 1.0	0.5 ± 1.0	0.0 ± 0.1	0.0 ± 0.1
<u>Active Co-Existing Health Conditions</u>					
Hypertension (%)	54.0	62.0	52.0 ^{**}	55.0	54.0
Hypercholesterolemia (%)	48.0	49.0	49.0	44.0	48.0
Incontinence (%)	19.0	30.0	24.0 [*]	18.0	9.0 ^{**}
Cardiovascular disease (%)	18.0	17.0	18.0	17.0	17.0
Thyroid disease (%)	16.0	16.0	13.0	23.0	20.0
Diabetes (%)	10.7	14.0	11.0	7.7	9.7
Cerebrovascular disease (%)	4.4	6.4	5.5	2.5	2.5

^a Among the 4,518 subjects who met the inclusion criteria, there were 4,087 subjects (90.5%) with complete data. Of the complete cases, there were 2,467 subjects with dementia (60.3%) and 1,620 subjects without dementia (36.6%).

^b Among 2,467 subjects with dementia, 374 (15%) had PIRx and 2,095 (85%) had no PIRx. Bivariate analyses (Pearson chi-square and Wilcoxon tests) were performed to examine the difference in distributions of subject characteristics between those with PIRx and those with no PIRx.

^c Among 1,620 subjects without dementia, 324 (20%) had PIRx and 1,296 (80%) had no PIRx. Bivariate analyses (Pearson chi-square and Wilcoxon tests) were performed to examine the difference in distributions of subject characteristics between those with PIRx and those with no PIRx.

^d Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory-Questionnaire. Factors analysis identified four factors: (1) agitation and irritability, (2) depression and anxiety, (3) motor disturbance and disinhibition, and (4) delusions and hallucinations. Scores were summed according to the factors (score range: 0 = no symptoms to 6 = severe in both symptoms).

^{*} $P < .050$;

100 > *P* **

Table 2
Two Multivariate Models of Associations between Subject Characteristics and Two
Definitions of Potentially Inappropriate Medication Use (PIRx): Model A – PIRx with Oral
Estrogens, and Model B – PIRx without Oral Estrogens.^a

Subject Characteristics	<u>Model A</u> PIRx with Estrogens		<u>Model B</u> PIRx without Estrogens	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
<u>Total Medication Use</u>				
One to two	1.00	-	1.00	-
Three to four	2.85	(2.12, 3.83) **	3.56	(2.46, 5.14) **
Five to six	4.81	(3.52, 6.59) **	5.67	(3.87, 8.31) **
Seven to Eight	8.62	(6.07, 12.24) **	10.57	(7.02, 15.94) **
Nine or more	12.73	(8.63, 18.77) **	14.91	(9.58, 23.19) **
<u>Dementia Status</u>				
No Dementia	1.00	-	1.00	-
Dementia	0.53	(0.39, 0.73) **	0.59	(0.42, 0.83) *
<u>Socio-Demographic Characteristics</u>				
<i>Age</i>	0.99	(0.97, 1.00) *	0.99	(0.98, 1.01)
<i>Sex</i> Female	1.00	-	1.00	-
Male	0.65	(0.53, 0.80) **	1.05	(0.84, 1.32)
<i>Race/Ethnicity</i> White (non-Hispanic)	1.00	-	1.00	-
Black (non-Hispanic)	1.01	(0.75, 1.35)	1.18	(0.87, 1.60)
Hispanic	0.77	(0.49, 1.22)	0.96	(0.60, 1.53)
Others (non-Hispanic)	1.29	(0.67, 2.51)	1.53	(0.76, 3.06)
<i>Education level</i> No high school degree	1.00	-	1.00	-
High school degree	1.15	(0.76, 1.73)	1.22	(0.80, 1.87)
College degree	0.81	(0.54, 1.23)	0.89	(0.58, 1.37)
Graduate degree	0.92	(0.60, 1.43)	0.96	(0.61, 1.51)
<i>Marital status</i> Married or living as married	1.00	-	1.00	-
Widowed, divorced, or separated	0.92	(0.52, 1.61)	1.00	(0.54, 1.85)
Never married or Other	1.09	(0.53, 2.22)	1.57	(0.73, 3.35)
<i>Living Arrangement</i> Alone	1.00	-	1.00	-
With spouse or partner	0.93	(0.53, 1.65)	0.95	(0.51, 1.76)
With other relatives or friends	1.08	(0.78, 1.49)	1.03	(0.73, 1.47)
With others	0.64	(0.30, 1.37)	0.70	(0.32, 1.56)
<i>Level of Dependence</i>				
Able to live independently	1.00	-	1.00	-
Need help with complex activities	0.90	(0.66, 1.24)	0.99	(0.71, 1.39)
Need help with basic activities	0.88	(0.61, 1.26)	0.98	(0.67, 1.44)
Completely dependent	0.78	(0.47, 1.28)	0.95	(0.57, 1.60)

Subject Characteristics	Model A PIRx with Estrogens		Model B PIRx without Estrogens	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
<u>Neuropsychiatric Symptoms^b</u>				
<i>Agitation and Irritability</i>	1.07	(0.98, 1.17)	1.08	(0.99, 1.18)
<i>Depression and Anxiety</i>	1.07	(0.98, 1.17)	1.05	(0.96, 1.16)
<i>Motor Disturbance and Disinhibition</i>	0.90	(0.80, 1.01)	0.93	(0.83, 1.05)
<i>Delusions and Hallucinations</i>	0.96	(0.85, 1.09)	0.94	(0.82, 1.07)
<u>Active Co-Existing Health Conditions</u>				
<i>Hypertension</i>	0.86	(0.71, 1.05)	0.99	(0.80, 1.22)
<i>Hypercholesterolemia</i>	0.71	(0.59, 0.85) **	0.75	(0.61, 0.91) *
<i>Incontinence</i>	1.40	(1.12, 1.75) *	1.51	(1.20, 1.91) **
<i>Cardiovascular disease</i>	0.71	(0.56, 0.90) *	0.76	(0.59, 0.98) *
<i>Thyroid disease</i>	0.79	(0.63, 1.00) *	0.76	(0.59, 0.98) *
<i>Diabetes</i>	0.65	(0.49, 0.87) *	0.71	(0.53, 0.96) *

^aRegression analyses were performed based on cases with complete data (N=4,087 patients).

^bNeuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory-Questionnaire. Factors analysis was conducted and four factors were identified: (1) agitation and irritability, (2) depression and anxiety, (3) motor disturbance and disinhibition, and (4) delusions and hallucinations. Scores were summed according to the factors (score range: 0 = no symptom to 6 = severe in both symptoms).

* $P < .050$;

** $P < .001$

Table 3
Among Dementia Patients Only, Two Multivariate Models of Associations between Patient Characteristics and Two Definitions of Potentially Inappropriate Medication Use (PIRx): Model A – PIRx with Oral Estrogens, and Model B – PIRx without Oral Estrogens.^a

Patient Characteristics	Model A PIRx with Estrogens		Model B PIRx without Estrogens	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
<u>Total Medication Use</u>				
One to two	1.00	-	1.00	-
Three to four	3.76	(2.14, 6.61)**	4.41	(2.34, 8.30)**
Five to six	6.44	(3.66, 11.36)**	6.39	(3.37, 12.10)**
Seven to Eight	12.61	(6.93, 22.94)**	13.22	(6.80, 25.70)**
Nine or more	17.35	(9.22, 32.65)**	18.43	(9.20, 36.91)**
<u>Likely Cause of Dementia</u>				
Probable Alzheimer's disease	1.00	-	-	-
Possible Alzheimer's disease	0.96	(0.64, 1.45)	1.09	(0.72, 1.65)
Lewy body dementia	0.45	(0.22, 0.92)*	0.47	(0.22, 0.98)*
Frontotemporal dementia	1.70	(0.84, 3.42)	1.84	(0.92, 3.70)
Parkinson's disease	0.55	(0.23, 1.36)	0.64	(0.26, 1.58)
Vascular dementia	0.81	(0.33, 2.00)	0.89	(0.38, 2.22)
Primary progressive aphasia	0.86	(0.30, 2.46)	0.80	(0.26, 2.49)
<u>Severity of Dementia^b</u>				
Very mild dementia	1.00	-	1.00	-
Mild dementia	0.81	(0.60, 1.09)	0.80	(0.59, 1.10)
Moderate dementia	0.65	(0.42, 0.99)*	0.69	(0.43, 1.03)
Severe dementia	0.85	(0.46, 1.58)	0.79	(0.42, 1.49)

^aRegression analyses are performed on only elderly patients with dementia who had complete data (2,467 patients). Table 3 only shows three patient characteristics of interest: total medication use, likely cause of dementia, and dementia severity. Other variables adjusted for in the multivariate analysis include the following: age, sex, race, education, marital status, living arrangement, level of dependence, neuropsychiatric symptoms, and selected comorbidities.

^bSeverity of dementia was assessed using the Clinical Dementia Rating scale (score range: 0.5=very mild dementia to 3.0 severe dementia)

* $P < .050$;

** $P < .001$