Functional Decline Associated with Polypharmacy and Potentially Inappropriate Medications in Community-Dwelling Older Adults with Dementia

Denys T. Lau, PhD;[1] Nathaniel D. Mercaldo, MS;[2] Joseph W. Shega, MD;[3] Alfred Rademaker, PhD;[4] and Sandra Weintraub, PhD[5]

[1] (**Corresponding Author**) Associate Professor, University of Illinois at Chicago, College of Pharmacy, Department of Pharmacy Administration. Address: 833 S. Wood Street (m/c 871), Chicago, IL 60612. (W) 312-355-5148. (F) 312-996-0868. Email: DTLau@uic.edu

[2] Biostatistician III, Vanderbilt University, Department of Biostatistics. Address: 1161 21st Ave South, S2323 MCN, Nashville, TN 37232. (W) 615-322-3997. (F) 615-322-4924. Email: nate.mercaldo@vanderbilt.edu

[3] Associate Professor, University of Chicago, Department of Medicine, Section of Geriatrics and Palliative Medicine. Address: 5841 S. Maryland Avenue, Chicago, IL 60637. (W) 773-702-5700. (F) 773-702-3538. Email: jshega@gmail.com

[4] Professor, Northwestern University, Feinberg School of Medicine, Department of Preventive Medicine. Address: 680 N. Lake Shore Drive, Suite 1400, Chicago, IL 60611. (W) 312-908-1970. (F) 312-908-3588. Email: rademaker@northwestern.edu

[5] Professor, Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Department of Neurology; and Clinical Core Director, Cognitive Neurology and Alzheimer's Disease Center. Address: 320 East Superior Street, Chicago, IL 60611. (W) 312-908-9023. (F) 312-908-8789. Email: sweintraub@northwestern.edu

ABSTRACT

This study provides empirical evidence on whether polypharmacy and potentially inappropriate prescription medications (PIRx, as defined by the 2003 Beers criteria) increase the likelihood of functional decline among community-dwelling older adults with dementia. Data were from the National Alzheimer's Coordinating Center, Uniform Data Set (9/2005-9/2009). Study sample included 1,994 community-dwelling subjects aged ≥65 with dementia at baseline. Results showed that subjects having ≥5 medications were more likely to have functional decline than subjects having <5 medications. However, the increased likelihood was only apparent in subjects who did not have PIRx. Instead of magnifying the associated risk as hypothesized, PIRx appeared to have a protective effect albeit marginally statistically significant. Therefore, increased medication burden may be associated with functional decline in community-dwelling older adults with dementia who are not prescribed with PIRx. More research is needed to understand which classes of medications have the most deleterious effect on this population.

Word count: 149 (<u>max</u>. 150)

Key Words (not in the title): Beers criteria; Alzheimer's disease; prescription drug utilization

INTRODUCTION

Ensuring appropriate medication use continues to be a major focus in health services research particularly among older adult populations.[1] Optimal prescribing in community-dwelling older adults with dementia may be even more important as memory loss, executive dysfunction, and underlying functional impairment can lead to problems following medication instructions, greater susceptibility to side effects, and difficulties in identifying and reporting adverse drug events.[2] Prior epidemiological studies on medication utilization in this population have examined the use of presumptive inappropriate medications, such as the Beers medications;[3, 4] co-administrations of cholinesterase inhibitors and anticholinergics;[5] underuse of medications to treat comorbid conditions;[6] and potential drug-drug and drug-disease interactions.[7] However, few studies have empirically examined the adverse health outcomes associated with such prescribing patterns in persons with dementia.[8, 9]

A high number of prescription medications (or polypharmacy) represents a significant risk factor in cognitively intact older adults for adverse health events, including hypoglycemia, fractures, hospitalization and death.[10] Furthermore, potentially inappropriate prescription medications (PIRx) have been linked with poorer health outcomes including adverse drug reactions, hospitalization, and falls.[11, 12] Perhaps the most cited explicit definition of PIRx, the Beers list has been developed by a national expert consensus panel and contains medications that generally are considered inappropriate for all older adults regardless of comorbidities.[13] Beers-defined PIRx use in cognitively intact older adults has been associated with the onset of cognitive decline, as well as psychological conditions including depression and malaise.[14]

Community-dwelling older adults with dementia may be at a higher risk for polypharmacy than those without dementia, and high number of prescription medications is significantly associated with PIRx .[3] Given the potential adverse health events associated with polypharmacy and PIRx,[12, 15] we aim to investigate the relationship between polypharmacy and Beers-defined PIRx with functional decline – a key, independent health-related risk factor for nursing home placement – among community-dwelling older adults with dementia.

Specifically, this study examines (1) whether polypharmacy is associated with functional decline among community-dwelling older adults; and (2) how this association may be modified by PIRx. We hypothesize that polypharmacy would increase the odds of functional decline, and PIRx would magnify this association. Findings of this study will have significant policy relevance because polypharmacy and adapted versions of the Beers list are currently employed as indicators of prescription quality by various national organizations, including the National Committee on Quality Assurance and the Centers for Medicaid and Medicare Services. Understanding the potential risk of functional decline related to medication use will further inform policymakers and clinicians in their evaluation of a high number of prescription medications and employment of the Beers list as a presumptive measure of prescribing quality in community-dwelling older adults with dementia.

METHODS

Data and Study Sample

Institutional Review Board approval for this study was obtained from the lead investigator's (DL) institution. This retrospective cohort study analyzed data from the

National Alzheimer's Coordinating Center (NACC), Uniform Data Set (UDS).[16] The UDS contains demographic and clinical data from subjects with and without dementia enrolled in 1 of 29 Alzheimer's Disease Centers (ADCs) across the United States funded by the National Institute on Aging (NIA). Since 2005, research-trained clinicians and staff followed standard protocols to collect data from respondents (patients and accompanying key informants) during their initial and follow-up ADC visits. All respondents (cognitively healthy controls and patients with dementia or mild cognitive impairment) are required to have an accompanying key informant (a family member or friend) to provide information about the participant, including medications taken.

At each ADC visit, data collected from respondents included, but were not limited to, patients' age, sex, race/ethnicity, education, marital status, and living arrangement. The names of all prescription medications used by the patients within the last two weeks of the ADC visit were self-reported by the respondents. Based on in-person clinical assessments, trained ADC clinicians and staff systematically evaluated each patient's dementia status (presence and severity of dementia according to the Clinical Dementia Rating [CDR] scale[17]); functional status (a single item about general level of dependence with activities of daily living); and a pre-determined list of comorbid conditions. (See "Measures" section for further details.)

This study examined subjects' first and second ADC visits captured in the UDS between 9/2005 and 9/2009, restricting the analysis to subjects aged 65 and older who were community-dwelling (i.e., living in an independent family residence or retirement community). To identify subjects with dementia at baseline, we included persons evaluated by an ADC clinician as meeting "the standard clinical criteria for dementia"[16]

and having CDR global scores ranging from 0.5 to 3.0 (very mild to severe dementia). Subjects without any prescription medication data were not included in the analysis because they represented an undistinguishable, heterogeneous group – those with missing data ("don't know" or "refused to answer") or those not taking any prescription medications – therefore, making interpretation difficult. At the final stage, we excluded a small portion of persons with missing values in any of their socio-demographic variables. The remaining 1,994 persons with baseline dementia were included in our study (**Table 1**).

Subjects *without* Baseline Dementia. For comparison purposes, we also assessed whether the associations between polypharmacy and PIRx with functional status varied by the presence or absence of baseline dementia. Among 1,988 persons who were clinically evaluated as having "normal cognition" and had a CDR global score of 0 (no dementia), our analysis found that 98.5% were able to live independently and the majority (97.4%) had the same functional status at both ADC visits. Due to the lack of variation in functional status between ADC visits, sufficient information for subjects with normal cognition was not available to reliably estimate regression parameters. We therefore did not report these findings; however, data are available upon request.

Measures

Dependent Variables: Functional Status

To indicate functional status at the second visit, we compared functional abilities between the two visits using the following response categories, regardless of living arrangement, (1) was able to live independently; (2) required assistance with complex activities of daily living such as paying bills, shopping, driving, and cooking; (3) required

assistance with basic activities of daily living such as eating, dressing, and bathing; or (4) was completely dependent on others. Ratings were based on the impact of cognitive impairment rather than physical impairment on functional skills. Functional decline was defined as any increase in functional dependence between the visits.

Independent Variable: Polypharmacy

The total number of prescription medications, excluding vitamins, herbal supplements, and topical agents, was counted per subject. Polypharmacy was defined with a dichotomous variable (yes/no) as having 5 or more prescription medications at the first ADC visit because prior research found that 5 or more medications substantially increased the risk of serious adverse drug events, including hospitalization and death.[19]

To assess the robustness of this definition of polypharmacy, we constructed an additional version of polypharmacy with a cutoff relative to the percentage distribution of total prescription medications in the study sample. We found that at the 85th percentile, the total number of prescription medications was 7; therefore, we also defined polypharmacy as having *7 or more medications* at the first ADC visit.

Independent Variable: PIRx

The 2003 Beers list[13] attempts to identify medications that are inappropriate because their potential health risks outweigh therapeutic benefits or because safer alternatives are available. Beers medications have three categories of PIRx for older adults: 1) medications that generally should be avoided in all patients; 2) medications at a specified dose that should not be exceeded; and 3) medications that should be avoided in patients with specified comorbid conditions.[13] Because of the data constraints of the UDS (e.g., incomplete information about drug dosage and duration,

and subjects' comorbid conditions), our analysis was limited to 44 agents/drug classes

of the Beers medications that generally should be avoided in all older patients

irrespective of their health conditions or indications. A person-level dichotomous

variable (yes/no) was constructed to indicate whether the subjects had any PIRx by

matching the Multum® drug codes (http://www.multum.com) of each medication

prescribed at the first ADC visit with the Multum codes corresponding to each of the

Beers medications.

<u>Other Characteristics</u>

Other baseline subject characteristics are listed in **Table 2**. Age was calculated

using date of birth and date of the first ADC visit. Race/ethnicity was combined into one

variable based on separate questions regarding race and Hispanic/Latino ethnicity. The

number of comoribid conditions per subject was based on affirmative responses to pre-

determined questions in the UDS about active co-existing diagnoses and recent

procedures (range: 0 to 7 comorbid conditions): hypertension, hypercholesterolemia,

thyroid disease, diabetes, incontinence (urinary or bowel), cardiovascular disease

(angioplasty, cardiac bypass procedure, congestive heart failure, or other

cardiovascular diseases), and cerebrovascular disease (stroke, transient ischemic

attack, or other cerebrovascular diseases). Additionally, based on the month and year of

ADC visits, the time lapse in years between the first and second visits was calculated.

Statistical Analysis

Baseline characteristics and functional status were tabulated. Categorical and

continuous variables were summarized as percentages and mean +/- 1 standard

deviation, respectively. To quantify the independent association between PIRx and

polypharmacy with subsequent functional status at follow-up visit, an ordinal logistic

regression model was developed (Model 1). Potential confounders that were controlled

for in the model included the patient's age, gender, race/ethnicity, number of comorbid

conditions, CDR global score, time between visits and baseline functional status. Then,

to determine whether PIRx modified the relationship between polypharmacy and

subsequent functional status, we included an interaction term between polypharmacy

and PIRx (i.e., having fewer than 5 medications with and without PIRx; and having 5 or

more medications with and without PIRx; Model 2). In both models, robust or sandwich

standard errors were calculated to account for the within ADC institutional correlations.

Estimated coefficients and 95% confidence intervals were exponentiated to reflect the

odds ratio of having a higher functional status score among those subjects receiving

PIRx (and 5 or more medications) versus those who did not. Proportional odds

assumptions were graphically assessed.[20] Furthermore, to assess the robustness of our

key findings, we performed sensitivity analysis using a different cutoff to define

polypharmacy (having 7 or more medications) and re-estimated both models. All

analyses were performed using R-version 2.10.0.[21]

RESULTS

Table 2 shows baseline characteristics of the study sample. The average age

was about 77 years old. Most subjects were male, non-Hispanic White, married, living

with at least one other person, and had at least a college degree. At the first ADC visit,

the average number of prescription medications in the study sample was 4.8 (SD=2.6).

About 49% had 5+ prescription medications and 22% had 7+ medications in the first

ADC visits. Comparable percentages were observed in the second visits: 48% had 5+

medications and 22% had 7+ medications (available upon request). Similar proportion

of subjects had Beers-defined PIRx in both visits: 16% in the first and 18% in the

second ADC visit. The five most commonly reported PIRx used were conjugated

estrogens, nifedipine, oxybutynin, fluoxetine, and doxazosin (data available upon

request). These most common PIRx remained unchanged between the first and second

visits.

Most subjects had very mild or mild dementia, and needed assistance with

complex or basic activities of daily living. Overall, about 59% (1173/1994) had the same

functional status at both ADC visits. By functional status, 43% of those who were able to

live independently at the first ADC visit were also able to live independently at the

second visit; 61% of those who required assistance with complex activities of daily living

at the first visit had the same functional status at the second visit; 62% of those who

required assistance with basic activities of daily living at the first visit had the same

functional status at the second visit; and 77% of those who were completely dependent

on others at the first visit were also completely dependent on others at the second visit

(**Table 3**). Similar patterns in functional decline between ADC visits were observed

among subjects with PIRx and those with polypharmacy (5+ or 7+ prescription

medications) – data available upon request.

Table 4 displays the key results of the multivariate regression analysis by

polypharmacy definition (5+ or 7+ prescribed medications). Model 1 shows that subjects

with having 5 or more medications at the first ADC visit had higher odds (OR=1.23, 95%

CI=1.01, 1.49) of having a lower functional status at the second visit than subjects

having fewer than 5 medications, controlling for PIRx, baseline functional status and

other factors. According to Model 2, among subjects with no baseline PIRx, those with 5 or more medications had higher odds (OR=1.27, 95% CI=1.03, 1.56) of having lower functional status in the next visit than those with fewer than 5 medications. However, compared to those subjects having fewer than 5 medications that were not PIRx, subjects with PIRx *regardless of polypharmacy* had statistically similar odds of having lower subsequent functional status (having < 5 medications: OR=0.94, 95% CI=0.58, 1.54; having 5+ medications: OR=0.96, 95% CI=0.72, 1.28). Similar patterns of association were observed when polypharmacy was redefined as having 7 or more medications. Appendix A contains results of all the other variables included in the regression models.

DISCUSSION

Necessary and proper use of medications are important health concerns among older adults, especially those with dementia, because of their increased potential for medication error, sensitivity to drug effects, and significant risk for nursing home placement.[22] Previously, we found that community-dwelling older adults with dementia generally had more prescription medications than those without dementia.[3] Employing the 2003 Beers list[13] as a presumptive measure of inappropriate medication use in older adults, we also found that polypharmacy was associated with elevated risk of PIRx, regardless of presence or absence of dementia. In this study, we used the UDS data to analyze the first and second ADC visits of community-dwelling older adults and empirically examined whether polypharmacy and PIRx in the initial visit were associated with functional decline – a significant risk factor for nursing home placement. Our hypothesis was partially supported.

Consistent with our hypothesis, we find that subjects with baseline dementia having 5 or more medications are more likely to have lower functional status in the subsequent visit than those subjects having fewer than 5 medications. However, the association with lower subsequent functional status exists only among subjects with 5 or more medications that do *not* include PIRx. Subjects with PIRx, regardless of having fewer or greater than 5 medications, have statistically similar odds of having lower functional status in the subsequent visit. The magnitude of these associations is similar when polypharmacy is redefined as having 7 or more medications.

In accordance to the growing body of literature,[23] our study suggests that the mere count of total prescription medications, in and of itself, may not necessarily indicate poor prescribing quality or predict worse functional outcome in older adults with dementia because subjects in this study with high number of medications are not more likely to have lower functional status if they have PIRx. Clinical efforts to reduce the prevalence of polypharmacy in this population therefore should entail a judicious process of weighing the risks against benefits of each medication prescribed according to the older patient's goal of care.

Furthermore, PIRx does not magnify the associated risk between having 5 or more (or, 7 or more) medications and subsequent functional status. These findings are counterintuitive because many Beers medications – including anxiolytics, antipsychotics, antidepressants, analgesics, antihistamines, stimulants, sedatives, and hypnotics – have known adverse psychotropic effects.[24] With regards to increasing the risk for functional decline, our study raises potential questions about using the Beers list as a presumptive measure of medication inappropriateness in community-dwelling older

adults with dementia. Future research should examine the impact of Beers medications on other health indicators, as well as investigate other criteria[25] or more specific sets of medications-to-avoid in this population. For example, estrogens have been found to increase the risk of the development and progression of dementia.[26] Other anticholinergic and sedative medications currently not included in the Beers criteria should be examined in this population due to their documented association with cognitive and function decline.[27]

This study has additional limitations. First, despite using the first and second ADC visits from UDS, observed relationships between polypharmacy and PIRx with dementia progression and functional decline cannot be assumed as causal. Without follow-up medication data in the analysis, it is possible that changes in polypharmacy or PIRx any significant risk factors of functional decline. Even though the average time between ADC visits is over one year, our findings indicate suggest that discontinuation of medications or PIRx between ADC visits may account for a small proportion of the study sample because (1) the 5 most commonly reported PIRx remain similar between the first and second ADC visits, and (2) the proportion of subjects with polypharmacy and PIRx increased only slightly between the first and second ADC visits. Although we controlled for a number of potential confounders including sociodemographic characteristics and health measures, our findings may reflect some unobserved factors. For example, this study examines medication prescriptions but not subjects' adherence to medications that may differ between subjects with and without dementia between ADC visits. In addition, despite controlling for a number of health measures, people who receive more medications may have greater severity in their health conditions that could

adversely affect their likelihood of functional impairment (rather than the medications they were taking). Second, although the UDS is one of the most comprehensive datasets currently available for studying patients with dementia across the United States, the UDS does not contain data from a random sample of patients; therefore, these findings cannot be interpreted as nationally representative. Recruitment procedures into ADCs may bias toward more-educated and higher-income older adults who received tertiary care from NIA-funded centers. More years of education has been associated with a lower likelihood of developing dementia.[28, 29] Third, data on medication use are reported by patients and key informants; consequently, there is potential bias toward underestimating medication utilization. Finally, over-the-counter medications were not accounted for in this study due to data quality but might be common among subjects with fewer prescription medications. For example, older adults with dementia may prefer taking over-the-counter medications, such as diphenhydramine for its sedative effects to prevent restlessness particularly at night. Our estimates of PIRx would be conservative by not accounting for Beers medications that are available over-the-counter. Similarly, because the data set does not contain dosage information, our estimates of PIRx did not include Beers-defined medications with dosage specifications (e.g., use of some of the benzodiazepines).

Prescribing practices with older adults involve a complex, evidence-based decision-making process in which clinicians must balance risks and benefits to achieve optimal health outcomes. Using national data from the UDS, this study is the first to our knowledge to empirically examine the potential adverse health outcomes associated with high number of prescription medications and Beers-defined PIRx in older adults

with dementia. Although polypharmacy increases the risk of PIRx, our study provides

little evidence that PIRx contributes to the observed association between polypharmacy

and lower functional status among subjects with dementia. Our results will need to be

replicated in other more generalizable populations. In summary, the necessity of high

number of prescription medications should be further examined in community-dwelling

older adults with dementia. Often employed as indicators of prescription quality, the

Beers list needs to be further investigated in regards to its adverse health effects in this

population.

ACKNOWLEDGMENTS

REFERENCES

1.   Healthy People 2020: Understanding and Improving Health. Office of Disease

      Prevention and Health Promotion, U.S. Department of Health and Human

      Services. 2020. Available at:

      http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=

      27. Accessed June 24, 2011.

2.   Bynum JP, Rabins PV, Weller W, et al. The relationship between a dementia

      diagnosis, chronic illness, medicare expenditures, and hospital use. *J Am Geriatr

      Soc.* 2004;52(2):187-194.

3.   Lau DT, Mercaldo ND, Harris AT, et al. Polypharmacy and potentially

      inappropriate medication use among community-dwelling elders with dementia.

      Alzheimer Dis Assoc Disord. 2010;24(1):56-63.

4.   Weston AL, Weinstein AM, Barton C, et al. Potentially inappropriate medication

      use in older adults with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci.*

      2010;65(3):318-21.

5.   Carnahan RM, Lund BC, Perry PJ, et al. The concurrent use of anticholinergics

      and cholinesterase inhibitors: rare event or common practice? *J Am Geriatr Soc.*

      2004;52(12):2082-2087.

6.   Kuzuya M, Masuda Y, Hirakawa Y, et al. Underuse of medications for chronic

      diseases in the oldest of community-dwelling older frail Japanese. *J Am Geriatr

      Soc.* 2006;54(4):598-605.

7. Giron MS, Wang HX, Bernsten C, et al. The appropriateness of drug use in an older nondemented and demented population. *J Am Geriatr Soc.* 2001;49(3):277-283.

8. Akishita M, Toba K, Nagano K, et al. Adverse drug reactions in older people with dementia. *J Am Geriatr Soc.* 2002;50(2):400-401.

9. Lu CJ, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am J Geriatr Psychiatry.* 2003;11(4):458-461.

10. Frazier SC. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. *J Gerontol Nurs.* 2005;31(9):4-11.

11. Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci.* 2007;62(10):1172-1181.

12. Jano E, Aparasu RR. Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother.* 2007;41(3):438-447.

13. Fick DM, Cooper JW, Wade WE, et al. 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(22):2716-2724.

14. Fick DM, Mion LC, Beers MH, et al. Health outcomes associated with potentially inappropriate medication use in older adults. *Res Nurs Health.* 2008;31(1):42-51.

15. Ellul J, Archer N, Foy CM, et al. The effects of commonly prescribed drugs in patients with Alzheimer's disease on the rate of deterioration. *J Neurol Neurosurg Psychiatry.* 2007;78(3):233-239.

16.   Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating

        Center (NACC) database: the Uniform Data Set. *Alzheimer Dis Assoc Disord.*

        2007;21(3):249-258.

17.   Morris JC. The Clinical Dementia Rating (CDR): current version and scoring

        rules. *Neurology.* 1993;43(11):2412-2414.

18.   Pfeffer RI, Kurosaki TT, Harrah CH, Jr., et al. Measurement of functional

        activities in older adults in the community. *J Gerontol.* 1982;37(3):323-329.

19.   Michocki R. Polypharmacy and Principles of Drug Therapy. Daly M, Weiss, BD,

        Adelman, AM, ed. *20 Common Problems in Geriatrics.* New York: McGraw-Hill.

        2001:69-81.

20.   Harrell FE. Regression Modeling Strategies With Applications to Linear Models,

        Logistic Regression, and Survival Analysis. New York: Springer, 2001.

21.   Development Core Team. R: A language and environment for statistical

        computing. Vienna, Austria. 2010. Available at http://www.R-project.org.

        Accessed June 24, 2011.

22.   Brauner DJ, Muir JC, Sachs GA. Treating nondementia illnesses in patients with

        dementia. *JAMA.* 28 2000;283(24):3230-3235.

23.   Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing

        quality in older people. *J Am Geriatr Soc.* 2006;54(10):1516-1523.

24.   Mort JR, Aparasu RR. Prescribing potentially inappropriate psychotropic

        medications to the ambulatory elderly. *Arch Intern Med.* 2000;160(18):2825-

        2831.

25.   Hamilton H, Gallagher P, Ryan C, et al. Potentially inappropriate medications

defined by STOPP criteria and the risk of adverse drug events in older

hospitalized patients. *Arch Intern Med.* 2011 Jun 13;171(11):1013-9.

26.   Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and

incidence of probable dementia and mild cognitive impairment in

postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004

Jun 23;291(24):2947-58.

27.   Hilmer SN, Mager DE, Simonsick EM, et al. Drug burden index score and

functional decline in older people. Am J Med. 2009 Dec;122(12):1142-1149.e1-2.

28.   Stern Y, Gurland B, Tatemichi TK, et al. Influence of education and occupation

on the incidence of Alzheimer's disease. *JAMA.* 1994;271(13):1004-1010.

29.   Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of

socioeconomic status and risk of incident Alzheimer's disease in a defined

population of older persons. *Archives of Neurology.* 1997;54(11):1399-1405.

TABLE 1. Sample Size According to Inclusion Criteria (Step-Wise)

Inclusion Criteria (Step-Wise)	N
1. All data	18,011
2. Have at least two ADC visits	9,869
3. Subjects diagnosed with dementia at baseline	3,238
4. CDR global score from 0.5 to 3.0 [a]	3,223
5. Age ≥ 65 at the first ADC visit	2,693
6. Community-dwelling subjects [b]	2,390
7. Have at least one prescription medication	2,057
8. Complete sociodemographic information [c] – **final study sample**	1,994

<u>Abbreviations</u>: ADC=Alzheimer's Disease Center; CDR= Clinical Dementia Rating

[a] CDR global score from 0.5 to 3.0 (very mild to severe dementia).
[b] Community-dwelling subjects include those living in an independent family residence or retirement community.
[c] Sociodemographic information include age, sex, race/ethnicity, education, marital status, and living arrangement.

TABLE 2. Baseline Characteristics of Study Sample (n = 1,994)[1]

Characteristics	
Age (mean±S.D.)	77.4±6.6
Sex (%)	
Female	49.2
Race/ethnicity (%)	
Non-Hispanic (NH) White	77.7
NH-Black	12.1
Hispanic	8.5
Others	1.7
Highest education (%)	
Less than high school	9.8
High school degree	31.9
College degree	36.4
Graduate degree	21.9
Marital status (%)	
Married/partnered	71.6
Not currently married	26.6
Never married	1.8
Living arrangement (%)	
Alone	13.0
With spouse or partner	70.1
With relative or friend	14.7
With others	2.2
Comorbid conditions [2]	
Number (mean±S.D.)	1.7±1.2
Time between visits	
Years (mean±S.D.)	1.1±0.3
Total Prescription Medications (%)	
Number (mean±S.D.)	4.8±2.6
Having 5+ meds	48.7
Having 7+ meds	21.8
PIRx (%)	
Any PIRx	16.2
CDR global score (%)	
0.5 – very mild dementia	31.0
1 – mild dementia	49.6
2 – moderate dementia	15.1
3 – severe dementia	4.3
Functional status at 1st Visit (%)	
Able to live independently	19.5
Need help with complex activities	51.7
Need help with basic activities	22.2
Completely dependent	6.6

Function and Polypharmacy/PIRx

Abbreviations: PIRx = potentially inappropriate medications; CDR = Clinical Dementia Rating scale; 5+ meds=five or more prescription medications; 7+ meds=seven or more prescription medications

[1] Baseline demographic characteristics were from the subject's 1st visit to the Alzheimer's Disease Center.
[2] Comorbid conditions included hypertension, hypercholesterolemia, incontinence, cardiovascular disease, thyroid disease, diabetes and cerebrovascular disease.

TABLE 3. Functional Status of Study Sample at Visits 1 and 2 to the Alzheimer's Disease Centers.

Functional status at 1st ADC Visit	**n=1,994**	**Functional status at 2nd ADC Visit (row percentage)**			
		Able to live independently	Need help with complex activities	Need help with basic activities	Completely dependent
Able to live independently	389	44%	41%	15%	1%
Need help with complex activities	1030	6%	61%	29%	4%
Need help with basic activities	443	3%	15%	62%	20%
Completely dependent	132	1%	3%	19%	77%

Abbreviation: ADC=Alzheimer's Disease Center

TABLE 4. Multivariate Models of the Association between Polypharmacy (5+ or 7+ Prescribed Medications) and PIRx on Functional Status (Presentation of Key Results) [1]

Functional Status at 2nd ADC Visit	O.R.	95% C.I.	P-Value
Polypharmacy = 5+ Medications			
Model 1			
1st visit having 5+ meds	1.23	(1.01, 1.49)	0.038
1st visit PIRx	0.81	(0.63, 1.05)	0.109
Model 2			
1st visit having <5 meds, no PIRx	1.00	--	--
1st visit having <5 meds, PIRx	0.94	(0.58, 1.54)	0.820
1st visit having 5+ meds, no PIRx	1.27	(1.03, 1.56)	0.025
1st visit having 5+ meds, PIRx	0.96	(0.72, 1.28)	0.794
Polypharmacy = 7+ Medications			
Model 1			
1st visit having 7+ meds	1.30	(1.03, 1.63)	0.026
1st visit PIRx	0.81	(0.64, 1.03)	0.084
Model 2			
1st visit having <7 meds, no PIRx	1.00	--	--
1st visit having <7 meds, PIRx	0.81	(0.57, 1.16)	0.256
1st visit having 7+ meds, no PIRx	1.30	(0.98, 1.72)	0.072
1st visit having 7+ meds, PIRx	1.06	(0.71, 1.58)	0.785

Note: ADC=Alzheimer's Disease Center; PIRx=potentially inappropriate prescription medications; 5+ meds=five or more prescription medications; <5 meds=fewer than five prescription medications; 7+ meds=seven or more prescription medications; <7 meds=fewer than seven prescription medications

[1] Variables adjusted for all the multivariate analyses included baseline subject characteristics at 1st visit to the Alzheimer's Disease Center: age group, sex, race/ethnicity, education, living arrangement, functional status, and number of comorbidities, CDR global score; and time between visits)

APPENDIX A. Multivariate Models of the Association between Polypharmacy (5+ or 7+ Prescribed Medications) and PIRx on Functional Status (Presentation of Full Results)

Functional Status at 2nd ADC Visit	O.R.	95% C.I.	P-Value
Polypharmacy = 5+ Medications			
Model 1			
1st visit having 5+ meds	1.23	(1.01, 1.49)	0.038
1st visit PIRx	0.81	(0.63, 1.05)	0.109
Age			
65-69	1.00	---	---
70-74	0.92	(0.75, 1.14)	0.471
75-79	1.00	(0.75, 1.33)	0.996
80-84	0.98	(0.76, 1.26)	0.871
>85	1.19	(0.84, 1.69)	0.332
Sex			
Female	1.05	(0.84, 1.32)	0.657
Race/ethnicity			
Non-Hispanic (NH) White	1.00	---	---
NH-Black	1.07	(0.81, 1.41)	0.653
Hispanic	1.23	(0.83, 1.83)	0.294
NH-Other	0.94	(0.35, 2.51)	0.906
Highest education			
College	1.00	---	---
Less than high school	0.90	(0.60, 1.34)	0.596
High school degree	0.95	(0.79, 1.14)	0.568
Graduate degree	0.97	(0.76, 1.23)	0.782
No. of comorbid conditions [1]	0.96	(0.90, 1.03)	0.276
Baseline CDR global score			
0.5 – very mild dementia	1.00	---	---
1 – mild dementia	2.20	(1.71, 2.82)	<0.001
2 – moderate dementia	7.07	(4.99, 10.03)	<0.001
3 – severe dementia	30.94	(14.65, 65.37)	<0.001

Baseline Functional Status			
Able to live independently	1.00	---	---
Need help with complex activities	4.66	(3.19, 6.80)	<0.001
Need help with basic activities	18.31	(9.66, 34.74)	<0.001
Completely dependent	127.55	(50.69, 320.93)	<0.001
Time between visits (year)	1.58	(1.16, 2.15)	0.004
Model 2			
1st visit having <5 meds, no PIRx	1.00	--	--
1st visit having <5 meds, PIRx	0.94	(0.58, 1.54)	0.820
1st visit having 5+ meds, no PIRx	1.27	(1.03, 1.56)	0.025
1st visit having 5+ meds, PIRx	0.96	(0.72, 1.28)	0.794
Age			
65-69	1.00	--	--
70-74	0.92	(0.75, 1.14)	0.466
75-79	1.00	(0.75, 1.33)	0.974
80-84	0.98	(0.76, 1.26)	0.865
>85	1.19	(0.84, 1.69)	0.339
Sex			
Female	1.05	(0.84, 1.33)	0.656
Race/ethnicity			
Non-Hispanic (NH) White	1.00	--	--
NH-Black	1.07	(0.81, 1.42)	0.637
Hispanic	0.95	(0.35, 2.53)	0.911
NH-Other	1.23	(0.83,1.83)	0.292
Highest education			
College	1.00	--	--
Less than high school	0.90	(0.60, 1.34)	0.596
High school degree	0.95	(0.79, 1.14)	0.560
Graduate degree	0.97	(0.76, 1.23)	0.782
No. of comorbid conditions [1]	0.96	(0.90, 1.03)	0.268
Baseline CDR global score			
0.5 – very mild dementia	1.00	--	--

1 – mild dementia	2.20	(1.71, 2.81)	<0.001
2 – moderate dementia	7.04	(4.97, 9.98)	<0.001
3 – severe dementia	30.91	(14.65, 65.24)	<0.001
Baseline Functional Status			
Able to live independently	1.00	--	--
Need help with complex activities	4.66	(3.20, 6.79)	<0.001
Need help with basic activities	18.43	(9.73, 34.89)	<0.001
Completely dependent	127.10	(50.46, 320.14)	<0.001
Time between visits (year)	1.58	(1.16, 2.15)	0.004
Polypharmacy = 7+ Medications			
Model 1			
1st visit having 7+ meds	1.30	(1.03, 1.63)	0.026
1st visit PIRx	0.81	(0.64, 1.03)	0.084
Age			
65-69	1.00	---	---
70-74	0.92	(0.75, 1.14)	0.464
75-79	1.01	(0.76, 1.34)	0.969
80-84	0.98	(0.77, 1.26)	0.899
>85	1.19	(0.84, 1.68)	0.339
Sex			
Female	1.06	(0.84, 1.34)	0.607
Race/ethnicity			
Non-Hispanic (NH) White	1.00	---	---
NH-Black	1.06	(0.80, 1.40)	0.698
Hispanic	0.94	(0.35, 2.53)	0.907
NH-Other	1.24	(0.84, 1.83)	0.283
Highest education			
College	1.00	---	---
Less than high school	0.88	(0.59, 1.32)	0.541
High school degree	0.95	(0.79, 1.15)	0.611
Graduate degree	0.97	(0.76, 1.23)	0.788
No. of comorbid conditions [1]	0.97	(0.91, 1.03)	0.274

Baseline CDR global score			
0.5 – very mild dementia	1.00	---	---
1 – mild dementia	2.19	(1.71, 2.82)	<0.001
2 – moderate dementia	7.07	(4.98, 10.03)	<0.001
3 – severe dementia	31.50	(14.59, 68.05)	<0.001
Baseline Functional Status			
Able to live independently	1.00	---	---
Need help with complex activities	4.69	(3.21, 6.84)	<0.001
Need help with basic activities	18.35	(9.65, 34.91)	<0.001
Completely dependent	130.97	(51.84, 330.90)	<0.001
Time between visits (year)	1.60	(1.17, 2.19)	0.003
Model 2			
1st visit having <7 meds, no PIRx	1.00	--	--
1st visit having <7 meds, PIRx	0.81	(0.57, 1.16)	0.256
1st visit having 7+ meds, no PIRx	1.30	(0.98, 1.72)	0.072
1st visit having 7+ meds, PIRx	1.06	(0.71, 1.58)	0.785
Age			
65-69	1.00	--	--
70-74	0.92	(0.74, 1.14)	0.463
75-79	1.01	(0.76, 1.34)	0.970
80-84	0.98	0.77, 1.26)	0.899
>85	1.18	(0.83, 1.69)	0.346
Sex			
Female	1.06	(0.84, 1.34)	0.609
Race/ethnicity			
Non-Hispanic (NH) White	1.00	--	--
NH-Black	1.06	(0.80, 1.40)	0.699
Hispanic	0.94	(0.35, 2.54)	0.907
NH-Other	1.24	(0.84, 1.83)	0.284
Highest education			
College	1.00	--	--
Less than high school	0.88	(0.59, 1.32)	0.541

High school degree	0.95	(0.80, 1.14)	0.608
Graduate degree	0.97	(0.76, 1.23)	0.788
No. of comorbid conditions [1]	0.97	(0.91, 1.03)	0.276
Baseline CDR global score			
0.5 – very mild dementia	1.00	--	--
1 – mild dementia	2.19	(1.71, 2.82)	<0.001
2 – moderate dementia	7.07	(4.98, 10.03)	<0.001
3 – severe dementia	31.51	(14.60, 67.99)	<0.001
Baseline Functional Status			
Able to live independently	1.00	--	--
Need help with complex activities	4.69	(3.22, 6.84)	<0.001
Need help with basic activities	18.35	(9.62, 34.99)	<0.001
Functional Status=Dependent	130.98	(51.99, 329.98)	<0.001
Time between visits (year)	1.60	(1.17, 2.19)	0.003

Abbrevations: ADC=Alzheimer's Disease Center; PIRx=potentially inappropriate prescription medications; 5+ meds=five or more prescription medications; <5 meds=fewer than five prescription medications; 7+ meds=seven or more prescription medications; <7 meds=fewer than seven prescription medications; CDR = Clinical Dementia Rating scale

[1] Comorbid conditions included hypertension, hypercholesterolemia, incontinence, cardiovascular disease, thyroid disease, diabetes and cerebrovascular disease.