Polypharmacy among older adults with dementia compared to those without dementia in the US

Matthew E. Growdon, MD, MPH[1,2]
Siqi Gan, MPH[1,2]
Kristine Yaffe, MD[2,3]
Michael A. Steinman, MD[1,2]

[1] Division of Geriatrics, University of California, San Francisco, CA
[2] San Francisco VA Medical Center, San Francisco, CA
[3] Departments of Neurology, Psychiatry, and Epidemiology and Biostatistics, University of California, San Francisco, CA

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Supplemental Information: Supplementary Methods

ICD-9 (2014-2015) Codes for Dementia

290.XX, 291.2, 292.82, 294.1, 294.10, 294.11, 294.20, 294.21, 331.19, 331.82, 331.0, 331.1X, 331.2, 046.1, 797

ICD-10 (2016) Codes for Dementia

G300, G301, G308, G309, G310, G311, G312, G319, F015, F028, F039, A810

In the main analyses, people with dementia (PWD) were identified as those with a diagnosis of dementia on the encounter form and/or those receiving an anti-dementia medication. For the diagnosis of dementia on the NAMCS patient record form, PWD could be identified by the indication of "Alzheimer's disease/Dementia" in the medical history section, if the practice responded affirmatively to the query, "Regardless of the diagnoses previously entered, does the patient now have Alzheimer's disease/Dementia?" NAMCS allows coding of up to five visit-related diagnosis codes specific to the sampled visit (including both acute and chronic conditions), using ICD-9 codes for 2014-2015 and ICD-10 codes for 2016. For ICD-10 codes, NAMCS limits the ICD code to the first four characters/digits in the public use file. Therefore, certain ICD-10 codes (such as G3183 for dementia with Lewy Bodies) could not be included, as other diagnoses that do not apply would be erroneously included when limiting to 4 characters/digits alone (e.g. G318 would also capture G3184 for mild cognitive impairment). We found that no new additional PWD were identified based on ICD diagnosis codes on top of the medical history section of the NAMCS patient record form. This is consistent with NAMCS survey form processing, given that U.S. Census Bureau field representatives, with input from

outpatient physicians and/or physician office staff, complete a computerized patient record form based on documentation from the sampled office visit (including physician diagnosis codes, which are converted to ICD codes following standardized procedures) and the electronic medical record. It is expected that this process would generally capture ICD-10 codes (for 2016) that we were unable to include in our list for the aforementioned reasons.

Highly anticholinergic medications

From Rhee et al 2019[1]: High-risk anticholinergic medications from the American Geriatrics Society Beers criteria[2] and Rudolph et al's Anticholinergic Risk Scale[3]

-Antidepressants (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, paroxetine, protriptyline, and trimipramine)
-Antimuscarinics (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium)
-Antihistamines (brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, doxylamine, hydroxyzine, meclizine, and triprolidine)
-Skeletal muscle relaxants (cyclobenzaprine and orphenadrine)
-Antispasmodics (belladonna alkaloids, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, and propantheline

Highly sedating medications

Based on sedative load model[4,5] – groups with sedative load of 2 (higher sedative burden)

-Hypnotics (all benzodiazepines)

-Nonbenzodiazepine sedative hypnotics (zolpidem, zaleplon, eszopiclone)

-Selected antiepileptic drugs (phenobarbital, gabapentin, pregabalin)

-Antipsychotics (all first-generation antipsychotics, quetiapine, olanzapine, clozapine)

-Antihistamine (promethazine, diphenhydramine)

-Additional antidepressant (doxepin)

References

1. Rhee TG, Choi YC, Ouellet GM, Ross JS. National Prescribing Trends of High-risk Anticholinergic Medications in Older Adults. J Am Geriatr Soc. 2018;66(7):1382-1387. doi:10.1111/jgs.15357

2. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults: 2019 AGS Beers Criteria® Update Expert Panel. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:10.1111/jgs.15767

3. Rudolph JL. The Anticholinergic Risk Scale and Anticholinergic Adverse Effects in Older Persons. Arch Intern Med. 2008;168(5):508. doi:10.1001/archinternmed.2007.106

4. Taipale HT, Bell JS, Uusi-Kokko M, Lönnroos E, Sulkava R, Hartikainen S. Sedative Load among Community-Dwelling People Aged 75 Years and Older. Drugs Aging. 2011;28(11):913-925. doi:10.2165/11597800-000000000-00000

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Supplementary Table S1: Regression analyses describing polypharmacy and highly anticholinergic and sedating medication prescribing among persons with dementia

Outcome	Proportion of visits among people with dementia 29.0 million visits (weighted)	Proportion of visits among people without dementia 780 million visits (weighted)	Crude OR (95% CI)	Adjusted OR (95% CI)
Polypharmacy -->=5 medications)	72% (0.64-0.79)	44% (0.42-0.47)	3.2 (2.2-4.6)	3.0 (2.1-4.3)
-->=10 medications)	43% (0.34-0.54)	20% (0.18-0.22)	3.1 (2.1-4.7)	2.8 (2.0-4.2)
At least one highly anticholinergic medication	16% (0.12-0.20)	8% (0.07-0.08)	2.2 (1.6-3.1)	1.9 (1.3-2.6)
At least one highly sedating medication	35% (0.24-0.46)	16% (0.15-0.17)	2.8 (1.7-4.7)	2.5 (1.6-3.9)
At least one of either of above	42% (0.32-0.52)	20% (0.19-0.22)	2.8 (1.8-4.3)	2.5 (1.7-3.6)

All results are adjusted for weights and survey design to produce nationally representative estimates. Adjusted ORs are the result of logistic regression with multivariate adjustment for age, sex, race, ethnicity, sampled physician specialty, new vs. follow-up status, geographic region, source of payment, and comorbidity count.

Supplementary Table S2: Regression analyses describing polypharmacy and highly anticholinergic and sedating medication prescribing among persons with dementia (primary care visits only)

Outcome	**Proportion of visits among people with dementia 17.1 million visits (weighted)**	**Proportion of visits among people without dementia 294 million visits (weighted)**	**Crude OR (95% CI)**	**Adjusted OR (95%CI)**
Polypharmacy --(>=5 meds) --(>=10 meds)	 75% (0.62-0.84) 48% (0.33-0.64)	 54% (0.50-0.59) 25% (0.22-0.28)	 2.5 (1.4-4.5) 2.8 (1.5-5.2)	 2.5 (1.4-4.4) 2.7 (1.6-4.7)
At least one highly anticholinergic medication	16% (0.11-0.24)	11% (0.10-0.12)	1.6 (1.0-2.6)	1.5 (0.97-2.4)
At least one highly sedating medication	39% (0.23-0.57)	20% (0.18-0.22)	2.5 (1.2-5.4)	2.4 (1.2-4.6)
At least one of either of above	47% (0.32-0.63)	26% (0.24-0.28)	2.5 (1.3-4.7)	2.3 (1.3-4.2)

All results are adjusted for weights and survey design to produce nationally representative estimates; the unweighted sample included 362 visits for PWD and 6,685 visits for PWOD. Adjusted ORs are the result of logistic regression with multivariate adjustment for age, sex, race, ethnicity, sampled physician specialty, new vs. follow-up status, geographic region, source of payment, and comorbidity count.

Supplementary Table S3: Medication use in people with versus without dementia, adjusted for age, sex, and comorbidity burden (primary care visits only)

Medication Category	Mean number of medications in use per visit		Probability of visit with at least 1 prescribed medication in use	
	Persons with dementia	Persons without dementia	Persons with dementia	Persons without dementia
Central Nervous System	1.8 +/- 0.14	0.59 +/- 0.04	85% (0.78-0.92)	35% (0.31-0.38)
--Cholinesterase inhibitors	0.50 +/- 0.05	-	50% (0.40-0.60)	-
--Antidepressants	0.36 +/- 0.05	0.19 +/- 0.01	31% (0.23-0.39)	15% (0.13-0.17)
--Anxiolytics, sedatives, hypnotics	0.29 +/- 0.06	0.20 +/- 0.02	26% (0.14-0.38)	17% (0.15-0.20)
--Antiepileptics	0.25 +/- 0.06	0.08 +/- 0.01	21% (0.10-0.31)	7% (0.06-0.08)
--Memantine	0.20 +/- 0.04	-	20% (0.13-0.31)	-
--Antipsychotics	0.08+/- 0.02	0.01 +/-0.005	7% (0.02-0.11)	1% (0.01-0.02)
Cardiovascular	2.1 +/- 0.16	2.0 +/- 0.09	77% (0.69-0.86)	67% (0.62-0.73)
Vitamins & Supplements	1.2 +/- 0.13	0.95 +/- 0.07	54% (0.45-0.63)	42% (0.37-0.47)
Other	0.93 +/- 0.15	0.71 +/- 0.04	47% (0.37-0.57)	41% (0.37-0.44)
Gastrointestinal	0.73 +/- 0.11	0.50 +/- 0.03	47% (0.33-0.62)	34% (0.30-0.38)
Analgesic	0.63 +/- 0.09	0.38 +/- 0.02	40% (0.30-0.49)	28% (0.26-0.31)
--Opioids	0.33 +/- 0.07	0.19 +/- 0.01	26% (0.17-0.35)	17% (0.15-0.20)
Diabetes	0.34 +/- 0.11	0.24 +/- 0.02	17% (0.10-0.23)	12% (0.10-0.14)
Hormone/Metabolic	0.36 +/- 0.04	0.38 +/- 0.02	32% (0.25-0.40)	30% (0.27-0.33)
Respiratory	0.30 +/- 0.07	0.31 +/- 0.02	18% (0.09-0.27)	19% (0.17-0.21)
Genitourinary	0.29 +/- 0.06	0.16 +/- 0.02	22% (0.09-0.34)	10% (0.08-0.12)
Coagulation Modifiers	0.25 +/- 0.06	0.16 +/- 0.01	17% (0.11-0.23)	13% (0.11-0.15)

Results show the predicted probabilities of taking at least one medication by medication category and the predicted value of the mean number of medications in use per visit by medication category, with age, sex, and comorbidity count standardized to their average values among PWD. All results are adjusted for weights and survey design to produce nationally representative estimates. Standard errors are presented for means and 95% CIs for percentages. Wilcoxon signed-rank tests support the predominance of higher mean number of medications in use per visit ($p=0.03$) and higher predicted probabilities of taking at least one medication by category ($p=0.007$) among PWD compared to PWOD.

Supplementary Table S4: Regression analyses describing polypharmacy and highly anticholinergic and sedating medication prescribing among PWD (removing anti-dementia medication from PWD definition)

Outcome	**Proportion of visits among people with dementia 18.3 million visits (weighted)**	**Proportion of visits among people without dementia 780 million visits (weighted)**	**Crude OR (95% CI)**	**Adjusted OR (95%CI)**
Polypharmacy --(>=5 meds) --(>=10 meds)	 63% (0.52-0.72) 38% (0.26-0.51)	 44% (0.42-0.47) 20% (0.18-0.22)	 2.1 (1.4-3.2) 2.5 (1.4-4.1)	 1.8 (1.2-2.7) 2.1 (1.3-3.4)
At least one highly anticholinergic medication	16% (0.10-0.24)	8% (0.07-0.08)	2.2 (1.3-3.7)	1.8 (1.1-3.0)
At least one highly sedating medication	37% (0.25-0.50)	16% (0.15-0.17)	3.1 (1.8-5.4)	2.8 (1.6-4.7)
At least one of either of above	43% (0.31-0.55)	20% (0.19-0.22)	3.0 (1.8-4.8)	2.6 (1.6-4.1)

All results are adjusted for weights and survey design to produce nationally representative estimates; the unweighted sample included 558 visits for PWD and 26,543 visits for PWOD. Adjusted ORs are the result of logistic regression with multivariate adjustment for age, sex, race, ethnicity, sampled physician specialty, new vs. follow-up status, geographic region, source of payment, and comorbidity count.

Supplementary Table S5: Medication use in people with versus without dementia, adjusted for age, sex, and comorbidity burden (removing anti-dementia medication from PWD definition)

Medication category	Mean number of medications in use per visit		Probability of visit with at least 1 prescribed medication in use	
	Persons with dementia	Persons without dementia	Persons with dementia	Persons without dementia
Central Nervous System	1.7 +/- 1.2	0.46 +/- 0.02	76% (0.68-0.84)	27% (0.25-0.29)
--Cholinesterase inhibitors	0.39 +/- 0.04	-	38% (0.31-0.46)	-
--Antidepressants	0.35 +/- 0.05	0.14 +/- 0.01	29% (0.20-0.38)	11% (0.10-0.12)
--Anxiolytics, sedatives, hypnotics	0.23 +/- 0.05	0.15 +/- 0.01	22% (0.13-0.31)	12% (0.11-0.14)
--Antiepileptics	0.26 +/- 0.07	0.07 +/- 0.005	21% (0.09-0.34)	6% (0.05-0.07)
--Memantine	0.19 +/- 0.03	-	19% (0.14-0.25)	-
--Antipsychotics	0.13 +/- 0.02	0.01 +/- 0.002	11% (0.07-0.16)	1% (0.007-0.01)
Cardiovascular	1.8 +/- 0.17	1.7 +/- 0.05	65% (0.56-0.74)	56% (0.53-0.60)
Vitamins & Supplements	0.84 +/- 0.09	0.77 +/- 0.04	41% (0.33-0.48)	33% (0.31-0.36)
Other	0.75 +/- 0.11	0.76 +/- 0.03	41% (0.33-0.50)	42% (0.40-0.45)
Gastrointestinal	0.59 +/- 0.10	0.40 +/- 0.02	37% (0.25-0.49)	27% (0.24-0.29)
Analgesic	0.49 +/- 0.08	0.31 +/- 0.01	31% (0.23-0.39)	22% (0.20-0.24)
--Opioids	0.25 +/- 0.05	0.17 +/- 0.01	22% (0.14-0.31)	15% (0.13-0.16)
Diabetes	0.30 +/- 0.11	0.22 +/- 0.01	11% (0.04-0.17)	10% (0.09-0.11)
Hormone/Metabolic	0.30 +/- 0.04	0.34 +/- 0.02	26% (0.19-0.34)	26% (0.24-0.28)
Respiratory	0.18 +/- 0.04	0.25 +/- 0.01	11% (0.06-0.16)	14% (0.13-0.15)
Genitourinary	0.22 +/- 0.06	0.15 +/- 0.01	15% (0.04-0.27)	9% (0.08-0.10)_
Coagulation Modifiers	0.22 +/- 0.07	0.16 +/- 0.01	14% (0.08-0.20)	13% (0.12-0.14)

Results show the predicted probabilities of taking at least one medication by medication category and the predicted value of the mean number of medications in use per visit by medication category, with age, sex, and comorbidity count standardized to their average values among PWD. All results are adjusted for weights and survey design to produce nationally representative estimates. Standard errors are presented for means and 95% CIs for percentages. Wilcoxon signed-rank tests support a trend towards predominance of higher mean number of medications in use per visit ($p=0.13$) and higher predicted probabilities of taking at least one medication by category ($p=0.03$) among PWD compared to PWOD.