Medication misuse and overuse in community dwelling persons with dementia

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Abstract

Background: Persons with dementia (PWD) have high rates of polypharmacy. While previous studies have examined specific types of problematic medication use in PWD, we sought to characterize a broad spectrum of medication misuse and overuse among community-dwelling PWD.

Methods: We included community-dwelling adults aged ≥66 in the Health and Retirement Study from 2008-2018 linked to Medicare and classified as having dementia using a validated algorithm. Medication usage was ascertained over the 1-year prior to an HRS interview date. Potentially problematic medications were identified by: 1) medication overuse including over-aggressive treatment of diabetes/hypertension (e.g., insulin/sulfonylurea with hemoglobin A1c<7.5%) and medications inappropriate near end of life based on STOPPFrail and 2) medication misuse including medications that negatively affect cognition and medications from 2019 Beers and STOPP Version 2 criteria. To contextualize, we compared medication use to people without dementia through a propensity matched cohort by age, sex, comorbidities, and interview year. We applied survey weights to make our results nationally representative.

Results: Among 1,441 PWD, median age was 84 (interquartile range=78-89), 67% female, and 14% Black. Overall, 73% of PWD were prescribed 1 potentially problematic medication with a mean of 2.09 per individual in the prior year. This was notable across several domains, including 41% prescribed 1 medication that negatively affects cognition. Frequently problematic medications included proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antihypertensives, and antidiabetic agents. Problematic medication use was higher among PWD compared to those without dementia with 73% vs. 67% prescribed 1 problematic medication (p=0.002) and mean of 2.09 vs. 1.62 (p<0.001), respectively.

Conclusion: Community-dwelling PWD frequently receive problematic medications across multiple domains and at higher frequencies compared to those without dementia. Deprescribing efforts for PWD should focus not only on potentially harmful central nervous system-active medications but also other classes such as PPIs and NSAIDs.

Keywords

cognitive impairment; dementia; polypharmacy; medication overuse; potentially inappropriate medication

INTRODUCTION

An estimated 6.5 million individuals aged 65 years and older were living with Alzheimer's disease and related dementias in the United States in 2022.[1] Persons with dementia (PWD) often have multiple comorbidities and high symptom burdens that contribute to a high prevalence of polypharmacy.[2,3] Polypharmacy is associated with several adverse health outcomes, including hospitalizations, emergency department visits, and increased mortality.[4,5] Drug-related problems are prevalent among PWD and contribute to unwanted hospitalizations at higher rates than those without dementia.[6-9] This is especially prominent in PWD due in part to increased susceptibility to medication side effects, drug-drug interactions, and difficulty with medication management leading to unintentional non-adherence and medication errors.[7,8,10]

Many medications may be problematic among PWD. For example, guidelines for diabetes management recommend less strict glycemic control for individuals with multimorbidity and limited life expectancy as the risks associated with certain antidiabetic agents, such as insulin and sulfonylureas, may outweigh the benefits of long-term tight glycemic control.[11,12] Similarly, many medications may cause net harm when used alone or in combination with other medications. For example, strongly anticholinergic and sedative-hypnotic medications have been associated with adverse outcomes including accelerated cognitive decline which is particularly worrisome in PWD who have decreased cognitive reserve.[13,14]

While several prior studies have documented a high prevalence of potentially inappropriate medication (PIM) use among PWD in the nursing home, less is known about the prevalence of medication misuse and overuse among the estimated ~70% of PWD living in the community.[15,16] Previous work has shown that community-dwelling PWD often receive PIMs at higher frequencies compared to individuals without dementia and receive more

medications across different medication classes.[17,18] However, less research has focused on a comprehensive approach to capturing a broad spectrum of potentially problematic medication use. Therefore, we sought to characterize the frequency and types of medication misuse and overuse in community-dwelling PWD across several domains, including overaggressive treatment of chronic conditions, medications inappropriate near the end of life, medications that negatively affect cognition, and medications to avoid based on consensus criteria. We additionally compare patterns of medication misuse and overuse among PWD to individuals without dementia.

METHODS

Study cohort

We included participants from the Health and Retirement Study (HRS) between 2008-2018, a nationally representative survey of US adults in which individuals are interviewed every 2 years.[19] We included community-dwelling individuals aged 66 with at least 12 consecutive months of Medicare Part A/B/D enrollment prior to a specific HRS interview date. Individuals were classified as having dementia based on a validated algorithm.[20,21] This algorithm, which includes predictors such as age, sex, cognitive tests, and physical functioning, was developed on HRS participants who underwent neuropsychological evaluations. It has displayed good accuracy in validation studies.[21]

Once an individual was classified as having dementia, they were classified with dementia for all subsequent waves. For individuals classified as having dementia with only one wave available, we used this wave as the index date to obtain medication information in the previous year. For individuals with multiple HRS interviews having a dementia classification, we selected one wave as the index date prioritizing the wave when the individual was selected for an enhanced face to face (EFTF) interview. Prioritizing EFTF interviews allowed us to collect information on hemoglobin A1c (HbA1c), cystatin C, and systolic blood pressure (SBP). Individuals are assigned to an EFTF interview every other wave (every 4 years).

Ascertainment of medication usage

We used a 1-year look-back period from a specific HRS interview date to ascertain medication usage which has been shown to have high sensitivity/specificity for identifying cross-sectional medication use (Supplementary Figure S1).[22] We obtained information on individual prescriptions, prescription dates, and days of supply. We linked Medicare Part D prescriptions to the Medi-Span database to collect information on drug name and drug class based on a Generic Product Identifier classification system. Unless otherwise specified, we considered medication usage as any days supplied (see Supplementary Methods for definitions of chronic medication use and overlapping prescriptions).

Measures of medication overuse and misuse

We defined two categories of potentially problematic medication use: medication overuse and misuse (Table 1). Measures within these domains were selected based on literature review of inappropriate medication use for older adults.[15,23,24] Information on how

individual criteria were operationalized is provided in the Supplementary Appendix and Methods.

Classification of medication overuse

Within the medication overuse domain, we included two subdomains: over-aggressive treatment of chronic conditions (diabetes/hypertension) and medications inappropriate near the end of life.[25,26] For overtreatment of diabetes/hypertension, we used information from the EFTF interview, in which an individual may have his or her SBP collected and/or blood drawn. We defined over-aggressive treatment of diabetes as prescriptions for insulin or sulfonylureas in the 6 months prior to when an individual with diabetes had a HbA1c<7.5%. We defined over-aggressive treatment of hypertension as prescriptions for antihypertensives in the 6 months prior to an average SBP<110 based on 3 measurements during the EFTF interview. As individuals may have indications for specific antihypertensives even if SBP<110 (e.g., beta-blockers in heart failure), we excluded individuals with specific diagnoses (Supplementary Methods, Table S1).

Medications inappropriate near the end of life were assessed using the Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy (STOPPFrail).[26] STOPPFrail involves medications that may be inappropriate for individuals with limited life expectancy (e.g., statins). We operationalized limited life expectancy as >50% 1-year mortality using the Gagne comorbidity index (score >9).[27]

Classification of medication misuse

Medication misuse was classified in two sub-domains: medications that negatively affect cognition and medications to avoid based on consensus criteria. Medications that negatively affect cognition included strongly anticholinergic medications (Table 7 of 2019 Beers criteria) and sedative-hypnotics based on previous studies and the Sedative Load Model (Supplementary Tables S2, S3).[23,28,29] The second sub-domain involved medications based on the 2019 American Geriatrics Society Beers Criteria for PIM Use in Older Adults and the Screening Tool of Older Persons' Prescriptions Version 2 (STOPP-V2).[23,24] Medications included in the 2019 Beers and STOPP-V2 criteria are categorized broadly as medications to avoid in older adults in general, medications to avoid given comorbidities (e.g., chronic kidney disease, heart failure), and medications that may be harmful when used in combination (e.g., opioids and benzodiazepines). Details are provided in Supplementary Methods. In brief, we used International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes in the 1-year look-back period from Medicare outpatient, inpatient, and Carrier files to identify comorbidities. For criteria based on creatinine clearance cut-offs, we used diagnosis codes or estimated glomerular filtration rate (eGFR) values obtained from a cystatin C measure from the EFTF interview.[30] For criteria involving overlapping medications or chronic use (e.g., >3 months continuous use), we used fill dates and days of supply. Given that we did not have detailed information on the indication for medication usage, our general approach was to omit criterion that were challenging to determine inappropriateness (Supplementary Methods).

Matched cohort

To place our results in context, we compared medication use for individuals with and without dementia. We performed 1:1 greedy nearest neighbor propensity score matching without replacement with a caliper distance of 0.25.[31,32] We 1:1 matched individuals with and without dementia by year of assessment, age, sex, and comorbidity count (sum score of self-reported hypertension, diabetes, cancer, heart disease, lung disease, stroke, and arthritis which covers a wide range of common chronic diseases among older adults). We matched on these characteristics, as done in previous studies, to obtain groups with broadly comparable characteristics with the goal of describing differential exposure to these medications rather than a more comprehensive matching strategy which runs the risk of over-controlling for contextual factors that often accompany a dementia diagnosis and are important factors in the lives of PWD.[17,18,33]

Outcomes

Our primary outcomes were 1) percentage of individuals receiving at least 1 medication flagged by our measures and 2) mean number of flagged medications per individual. We report these metrics overall and across individual domains. As some medications were flagged under multiple domains (e.g., lorazepam under medications that negatively affect cognition, 2019 Beers, and STOPP-V2), we counted each medication only once when reporting the overall measure.

Statistical analysis

Data were analyzed incorporating survey weights to account for the HRS complex survey design. Since some individuals did not have a HbA1c or SBP available (e.g., might not have participated in an EFTF interview), we used multiple imputation (MI) to create 10 datasets with imputed HbA1c and SBP values to ascertain potentially problematic medication use in the over-aggressive treatment of diabetes/hypertension sub-domain (Supplementary Methods). In the matched cohort, given that individuals could be included in the pool of individuals without dementia multiple times across different interview years, we accounted for repeated measures and intra-individual correlation using a generalized estimating equation (GEE) model. To compare percentage of individuals with 1 flagged medication, we calculated odds ratios and p-values using GEE models with binomial distribution. To compare mean number of flagged medications, we calculated incidence rate ratios and p-values using GEE models with Poisson distribution.

We performed several sensitivity analyses (Supplementary Methods). First, we created 2 additional cohorts: matched only on year of assessment and matched on several additional factors (e.g., functional impairments, healthcare utilization). Second, we repeated our analysis using inverse probability of treatment weighting (IPTW). Third, we performed an analysis that included and excluded criteria that either only applied to PWD or differed between persons with and without dementia (Supplementary Table S4). Fourth, we performed an analysis in which the non-dementia cohort was not preferentially selected based on an EFTF. Fifth, we conducted an index of local sensitivity to nonignorability (ISNI) analysis to assess the robustness of multiple imputation. Analyses were conducted using SAS 9.4 (SAS Institute Inc.) and STATA 17.0 (Stata Corp). The statistical significance

threshold was 2-sided p-value<0.05. The study was reviewed and approved by the University of California, San Francisco Committee on Human Research.

RESULTS

Supplementary Figure S2 shows the flow chart to identify participants. The final cohort included 1,475 individuals classified with probable dementia during the study period and 9,199 individuals in the pool of individuals without dementia (Supplementary Table S5). In the matched cohort involving 1,441 PWD, the median age was 83.6 (interquartile range=78.1-89.0), 947 (survey-weighted 66.5%) were female, 289 (survey-weighted 14.4%) identified as non-Hispanic Black, and 246 (survey-weighted 14.1%) identified as Hispanic (Table 2). Compared to individuals without dementia, PWD in the matched cohort had a greater number of functional dependencies. PWD were prescribed a similar number of unique medications with 28-day supply in the prior year (median 6.6 vs. 6.5).

Overall, across all domains, 73% of PWD received 1 potentially problematic medication (Table 3, Supplementary Table S6). The overall mean number of flagged medications per PWD was 2.09 (Figure 1). Problematic medication use was prominent across several domains. For example, the percentage of PWD receiving 1 flagged medication and mean number of flagged medications was 17% and 0.18 for over-aggressive treatment of diabetes/ hypertension, 41% and 0.61 for medications that negatively affect cognition, 60% and 1.53 for 2019 Beers, and 66% and 1.32 for STOPP-V2, respectively. Among the 85 (survey-weighted 5.9%) PWD eligible for the criteria of medications inappropriate near the end of life using STOPPFrail, 18.5% had 1 flagged medication with a mean of 0.33 medications. Supplementary Table S7 shows the number and percentage of individuals with diabetes and hypertension who met criteria for over-aggressive treatment of these conditions. Notably, ~40% of individuals with diabetes and A1c<7.5% with and without dementia were receiving insulin/sulfonylureas.

Figure 2 shows the most frequent medications among PWD identified as potentially problematic. This included medications from multiple classes, including proton pump inhibitors (PPIs), gabapentin, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, selected antihypertensives and antidiabetic agents, antihistamines/antiemetics (e.g., meclizine and promethazine), and urinary anticholinergics.

In the matched cohort, the percentage of individuals with 1 flagged medication overall was 73% among PWD and 67% among persons without dementia (p=0.002) (Table 3). The mean number of flagged medications overall was 2.09 vs. 1.62 (p<0.001) among those with and without dementia, respectively (Figure 1). In general, PWD received more potentially problematic medications across domains. Supplementary Figure S3 shows the distribution of potentially problematic medications among individuals with and without dementia.

Sensitivity analyses

In the cohort matched on year of assessment, PWD were older and had more comorbidities and functional impairments (Supplementary Table S8). The cohort matched on several factors showed similar characteristics between persons with and without dementia

(Supplementary Table S9). Our primary results were essentially unchanged in the cohort matched on year of assessment (Supplementary Table S10). In the cohort matched on several additional factors, persons with and without dementia had a similar mean number of flagged medications (2.09 vs. 2.04, p=0.72) and similar percentage of individuals with 1 flagged medication (73% vs. 71%, p=0.37) (Supplementary Table S11).

Our primary results were similar in the sensitivity analysis using IPTW (Supplementary Table S12). Including and excluding criteria that were specific to individuals with dementia did not significantly change the overall results (Supplementary Table S13). One notable difference was in the STOPP-V2 criteria where the mean number of flagged medications changed from 1.32 vs. 0.96 (p<0.001) to 0.98 vs. 0.94 (p=0.49) among persons with and without dementia, respectively. An analysis where individuals were not preferentially selected based on the EFTF interview showed similar overall results (Supplementary Table S14). The ISNI sensitivity analysis suggested that the MI results were reliable for the analysis (Supplementary Methods, Tables S15 & S16, Figure S4).

DISCUSSION

In this nationally representative study, community-dwelling PWD were frequently prescribed medications that may indicate medication misuse and overuse across a variety of domains. Problematic medication use spanned many medication classes with the most prominent including PPIs, NSAIDs, opioids, antihypertensives, and antidiabetic agents. In a matched cohort, PWD received more of these potentially problematic medications and at a higher frequency across most domains compared to persons without dementia. We extend the results of previous studies by taking a more comprehensive approach to show the broad spectrum of potentially problematic medications among community-dwelling PWD.

Identification of problematic medication use in PWD has primarily focused on individuals with advanced dementia in the nursing home.[16] The few studies among community-dwelling PWD have predominantly used populations outside the United States or attending specialized memory care clinics or focused on overall prescribing of medications.[16-18,34] A 2020 review of 6 studies reported a pooled prevalence for PIM use among community-dwelling PWD of 31% with estimates ranging from 13.9% to 54.4%.[16] Among individual studies, a 2014 Danish study found that PIM use for community-dwelling PWD was 38.1% based on red-yellow-green list and 20.4% based on the German PRISCUS list.[18] The most frequent PIMs included NSAIDs (11.4%), quetiapine (8.1%), and nitrofurantoin (7.2%). A retrospective cohort involving 11,175 PWD aged 65 in England found a PIM prevalence of 73% using STOPP-V2, with frequent contributing medications including anticholinergics, duplicate drug class prescriptions, and NSAIDs.[33]

We extend the results of these studies through a more comprehensive assessment of medication misuse and overuse. PIMs only capture a small percentage of inappropriate prescribing. We identified different situations in which medications may be inappropriate, such as over-aggressive treatment of diabetes/hypertension and those inappropriate in the presence of specific diagnosis codes. Additionally, we defined medication inappropriateness based on comorbidities, duration of use, and clinical/laboratory indicators rather than

simply flagging its presence. We show that potentially problematic medication use in PWD not only involves central nervous system (CNS)-active medications (e.g., benzodiazepines/antipsychotics) but also other classes of medications, including PPIs, NSAIDs, antihypertensives, and antidiabetic agents.

The high frequency of medication overuse and misuse among PWD is particularly concerning. First, PWD are at high risk for drug-related problems.[7,8,35] PWD are more likely to be hospitalized due to adverse drug events and medication errors than persons without dementia with one study identifying that anticoagulants and opioids contributed to the majority of admissions.[6] Additionally, many of the potentially problematic medications highlighted in our study, such as strongly anticholinergic medications and sedative-hypnotics, have been linked with accelerated cognitive decline, hospitalizations, and death.[13,14,36] Second, PWD may be less likely to benefit from aggressive management of chronic conditions due to limited life expectancy. Clinical guidelines for chronic diseases such as diabetes frequently emphasize the need to tailor treatment goals as shorter-term harms of medications may outweigh longer-term benefits.[11,12,37] Third, high rates of medications frequently prescribed for symptom management, such as PPIs, NSAIDs, and antihistamines/antiemetics, can also be problematic among PWD. PPIs are frequently prescribed for long-term use without a compelling indication, contributing to increased medication burden, drug-drug interactions, vitamin deficiencies, and possibly fractures/ infections.[38] Many antihistamines and anticholinergic antiemetics frequently prescribed in our cohort (e.g., meclizine and promethazine), are not recommended given adverse effects, lack of significant benefit, and/or presence of safer alternatives.

To place our results in context, we compared problematic medication use among PWD to persons without dementia. PWD received more potentially problematic medications and at a higher frequency across most domains. One explanation is more frequent prescribing of sedative-hypnotics and anticholinergic antidepressants/antipsychotics due to behavioral issues and mood disorders in PWD.[39] Second, PWD are more likely to have problematic medication combinations despite similar number of overall medications. This was evidenced by a higher number of opioids used in combination with gabapentin/benzodiazepines or the presence of 3 CNS-active medications similar to previous studies.[40,41] Third, management of the same comorbidity may differ in these two groups. For example, PWD may have more difficulty managing lower urinary tract symptoms with behavioral interventions leading to higher use of urinary anticholinergics.[42]

Our study indicates that efforts to reduce polypharmacy in PWD should target a wide range of medications contributing to medication misuse and overuse. The majority of PWD are willing to deprescribe medications if a doctor said it was possible.[43,44] Given the broad range of medications flagged as potentially inappropriate, clinicians and pharmacists should take a holistic approach to deprescribing efforts.[45] On an individual level, patients and families should be asked about which medications they feel are most problematic or burdensome. This can be followed by a comprehensive medication assessment that assesses the efficacy and benefits/harms of each medication considering an individual's values and remaining life expectancy. From a health systems perspective, potentially problematic medications identified in our study with high frequency such as PPIs, NSAIDs, opioids,

gabapentin, and antihypertensives/diabetes medications may be potential common targets for deprescribing. Many websites and educational brochures are available that can assist in this shared decision-making process.[46,47] Deprescribing decisions must be individualized based on factors such as values/preferences, careful assessment of benefits/harms, and feasibility of alternative approaches to managing conditions (e.g., chronic pain). Results from deprescribing interventions among PWD highlight the need to identify subgroups of PWD most likely to benefit from these interventions which is a topic for future research.[48]

The primary strength of our study is the utilization of a nationally representative sample of community-dwelling PWD linked to detailed medication data. Our comprehensive approach to medication classification highlights a broad spectrum of medication inappropriateness. A few limitations should be acknowledged. First, participants were classified as having dementia using a validated algorithm which may be subject to misclassification. However, we feel that our cohort represents the typical phenotype of community-dwelling PWD in which a thorough evaluation at a specialized memory clinic has not been performed and the diagnosis is often based on basic cognitive testing and functional decline. While the dementia classification algorithm has shown good accuracy in validation studies against gold standard dementia diagnoses, it may be less accurate among racial/ethnic minorities and less-educated individuals.[21] Second, we omitted several criteria either due to limited information (e.g., lack of data on sodium values) or difficulty in operationalizing the criteria. We chose a conservative approach, omitting criterion that were challenging to determine whether the medication was potentially inappropriate. We acknowledge that some medications identified as potentially problematic may be reasonable choices based on individual circumstances. Our aim was to identify medications often considered misused/ overused and frequently represent candidates to consider for discontinuation. Third, we were not able to collect information on medications commonly obtained over the counter, such as aspirin, other NSAIDs (e.g., ibuprofen), iron, and vitamins. Fourth, our measure of over-aggressive treatment of hypertension/diabetes may be an over-estimate given the 6-month look-back period from date of HbA1c/SBP. However, previous studies have highlighted low deintensification rates in similar settings.[49] Finally, we included individuals who were enrolled in Medicare Part D and with 1 claim in the previous year. We also did not have information on individuals enrolled in Medicare Advantage which is an important area for future research given limited studies on problematic medication use.[50]

CONCLUSIONS

Community-dwelling PWD frequently receive medications considered potentially misused and overused across several domains, including overaggressive treatment of hypertension/ diabetes, medications that negatively affect cognition, and medications to avoid based on consensus criteria. Compared to individuals without dementia, PWD were more likely to receive these medications. Understanding the extent of problematic medication use in PWD is the first step in guiding interventions to areas most likely to reduce problematic prescribing. Our results suggest that deprescribing efforts in this population should focus not just on harmful CNS-active medications but on the frequent use of medications across different classes, such as PPIs and NSAIDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Key Points:

- In this national study, community-dwelling persons with dementia frequently received medications classified as potentially misused and overused based on a broad set of criteria such as over-aggressive treatment of diabetes/ hypertension, medications that negatively affect cognition, and medications from consensus criteria (2019 Beers and STOPP Version 2).

- Medications frequently identified as potentially problematic spanned multiple classes with the most common including proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antihypertensives, and antidiabetic agents (e.g., when used in the setting of controlled blood pressure/hemoglobin A1c or for other problematic reasons).

- Compared to persons without dementia, persons with dementia were more likely to receive these potentially problematic medications across several domains.

Why does this matter?

Understanding the frequency and types of potentially problematic medication use among community-dwelling older adults with dementia is the first step in guiding interventions to areas most likely to reduce problematic prescribing. Our results suggest that deprescribing efforts in this population should focus not only on potentially harmful central nervous system-active medications but also other classes such as PPIs and NSAIDs.
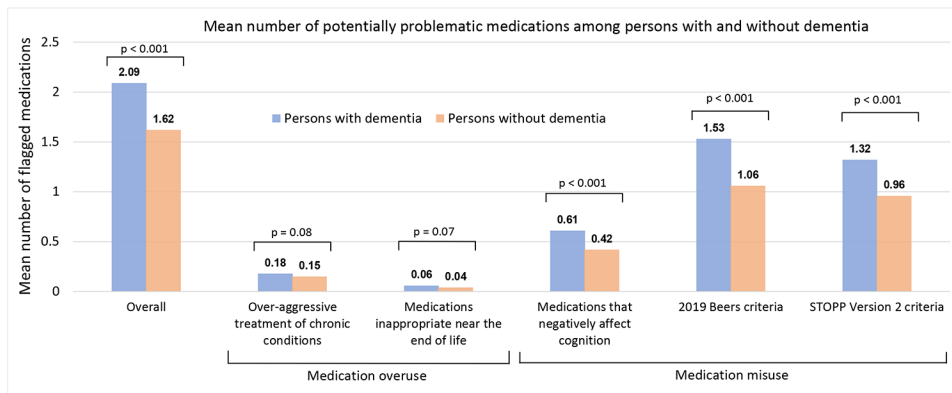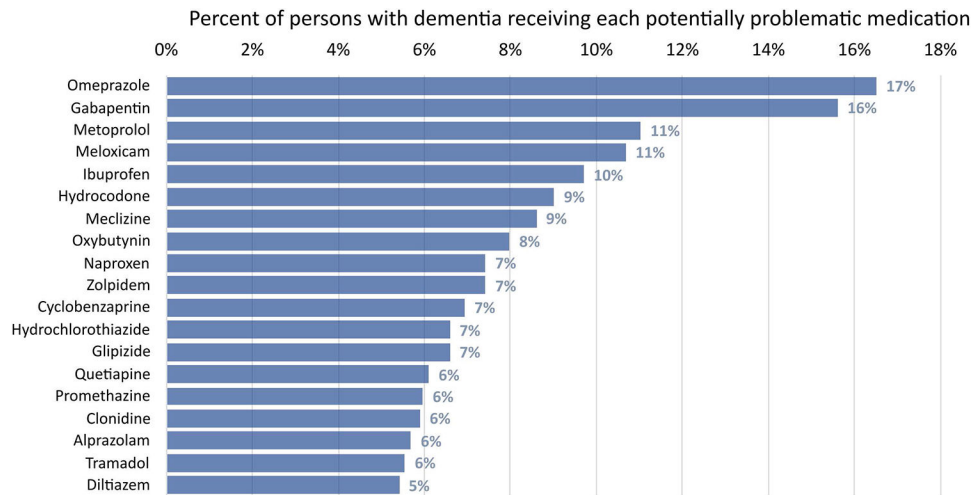
Figure 1:

Mean number of medications identified as potentially problematic among community-dwelling older adults with and without dementia overall and by domain in the primary cohort matched on age, sex, comorbidity count, and year of assessment[a]

Abbreviations: STOPP-V2, Screening Tool of Older Persons' Prescriptions Version 2

a As some medications were flagged under multiple domains (e.g., lorazepam under medications that negatively affect cognition, 2019 Beers, and STOPP-V2), we counted each medication only once when reporting the overall summary measure.

Percent of persons with dementia receiving each potentially problematic medication

Figure 2:

Medications most frequently identified as potentially problematic among community-dwelling older adults with dementia in the primary cohort (n=1,441)[a]

a Certain medications could be flagged as potentially problematic in multiple ways. For example, proton pump inhibitors could be flagged based on use for >8 weeks in the absence of reason for continued use (e.g., diagnosis code for Barrett's esophagus). Gabapentin could be flagged under the "medications that negatively affect cognition" domain (as a sedative-hypnotic) or through the 2019 Beers criteria (overlapping prescription of gabapentin/opioid or combination of 3 central nervous system active drugs). Non-steroidal anti-inflammatory drugs like meloxicam and naproxen could be flagged when used for prolonged durations (e.g., consecutive fills for >90 days), when used with certain diagnosis codes (e.g., gastric ulcer), in advanced chronic kidney disease, or when used with anticoagulants. Antihypertensives (e.g., metoprolol, clonidine) and antidiabetic agents (e.g., glipizide) could be flagged under the "over-aggressive treatment of chronic conditions" domain (e.g., systolic blood pressure <110 on antihypertensive without alternative indication), when used in combination with another medication (e.g., beta-blocker and verapamil/diltiazem), or when used in setting of specific conditions (e.g., beta-blocker with history of heart block).

Table 1:

Domains used to assess potentially problematic medication use

Domain	Measure type	Measure sources	Examples
Medication overuse	Over-aggressive treatment of chronic conditions	Choosing Wisely, clinical guidelines[12,25]	• Diabetes: Hemoglobin A1c < 7.5% and prescription for insulin or sulfonylurea • Hypertension: Average SBP < 110 mmHg and prescription for certain antihypertensive medications (without other compelling indication)
	Medications inappropriate near the end of life	STOPPFrail Criteria[26]	• Lipid-lowering therapies, bisphosphonates
Medication misuse	Medications that negatively affect cognition	Strongly anticholinergic medications from 2019 Beers criteria Table 7, Sedative Load Model[23,28]	• Strongly anticholinergic medications: certain antihistamines, urinary anticholinergics, certain antidepressants • Sedative-hypnotics: benzodiazepines, nonbenzodiazepine hypnotics
	Drugs to avoid criteria	2019 Beers and STOPP Version 2 criteria[23,24]	• Drugs in general: long-acting sulfonylureas • Drug-disease interaction: thiazolidinediones in heart failure • Drug-drug interaction: concurrent use of 3 CNS-active medications • Drugs in the setting of reduced kidney function: Duloxetine if CrCl <30

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; SBP, systolic blood pressure; STOPP, Screening Tool of Older Persons' Prescriptions; STOPPFrail, Screening Tool of Older Persons' Prescriptions in Frail adults with limited life expectancy

Table 2:

Baseline characteristics of community-dwelling older adults with and without dementia enrolled in the Health and Retirement Study from 2008-2018 included in the primary cohort matched on age, sex, comorbidity count, and year of assessment

Characteristic	Persons with dementia (n = 1,441) Number (weighted %)[a]	Persons without dementia (n = 1,441) Number (weighted %)[a]	SMD
Age in years, median (IQR)	83.6 (78.1-89.0)	83.1 (77.2-88.4)	0.001
Female sex	947 (66.5%)	947 (65.4%)	−0.02
Race/Ethnicity			0.42
Non-Hispanic White	876 (69.2%)	1160 (86.1%)	
Non-Hispanic Black	289 (14.4%)	150 (6.5%)	
Hispanic	246 (14.1%)	105-110 (~6.0%)[b]	
Other	30 (2.3%)	<25 (<1.5%)[b]	
Marital status (%)			−0.07
Married or partnered	554 (37.5%)	603 (41.3%)	
Single or widowed	887 (62.5%)	838 (58.7%)	
Lives alone (%)	448 (34.2%)	626 (45.8%)	−0.24
Self-reported comorbidities			
Cancer	338 (23.0%)	367 (24.3%)	−0.03
Diabetes	486 (31.0%)	449 (31.2%)	−0.005
Heart disease	639 (44.3%)	686 (48.1%)	−0.08
Hypertension	1099 (74.3%)	1121 (76.7%)	−0.05
Lung disease	218 (16.6%)	226 (16.1%)	0.01
Median (IQR) number of IADL dependencies (range 0-5)	1.8 (0-3.7)	0 (0-0)	0.02
Median (IQR) number of ADL dependencies (range 0-6)	0.8 (0-3.2)	0 (0-0.1)	0.01
Median (IQR) number of chronic medications[c]	6.6 (4.1-10.2)	6.5 (4.0-10.1)	0.001
Polypharmacy (prescription for 5 chronic medications)[c]	1103 (75.9%)	1100 (74.7%)	0.03
1-year predicted mortality risk >50% from Gagne index	85 (5.9%)	46 (3.4%)	0.12

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; IQR, interquartile range; SMD, standardized mean difference

[a] The numbers in each column represent the raw unweighted number of individuals within each cohort with a particular characteristic. The weighted percentages in each column represent the column percent based on the weighted sample size after using national survey weights from the Health and Retirement Study

[b] Results are presented in this manner due to the Centers for Medicare and Medicaid Services (CMS) cell suppression size policy which sets the minimum threshold for the display of CMS data. This was necessary as the "Other" category involved <25 individuals.

[c] The number of medications was assessed by looking at the number of unique medications with at least a 28-day supply for an individual in the 1-year look back period.

Table 3:

Frequency of potentially problematic medication use among community-dwelling older adults with and without dementia overall and by domain in the primary cohort matched on age, sex, comorbidity count, and year of assessment

Medication domain	Percent with at least 1 potentially problematic medication		
	Persons with dementia (n = 1,441)	Persons without dementia (n = 1,441)	P-value
Overall	73%	67%	p = 0.002
Medication overuse			
Over-aggressive treatment of diabetes and hypertension	17%	14%	p = 0.07
Medications inappropriate near end of life (based on STOPPFrail)[a]	4%	2%	p = 0.02
Medication misuse			
Medications that negatively affect cognition (e.g., strongly anticholinergic, sedative-hypnotic)	41%	30%	p < 0.001
2019 Beers criteria	60%	51%	p < 0.001
STOPP Version 2 criteria	66%	53%	p < 0.001

Abbreviations: STOPP, Screening Tool of Older Persons' Prescriptions; STOPPFrail, Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy

[a.] The number of individuals eligible for the criteria of medications inappropriate near the end of life based on Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy (STOPPFrail) (i.e., predicted 1-year mortality risk >50% based on the Gagne index) was 85 (5.9%) among PWD and 46 (3.4%) among persons without dementia. Among the 85 PWD eligible for this criteria, the percentage with 1 flagged medication was 18.5% for a mean of 0.33 flagged medications. Among the 46 persons without dementia eligible for this criteria, the percentage with 1 flagged medication was 21.9% for a mean of 0.29 flagged medications.