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Prevalence of Central Nervous System–Active Polypharmacy Among Older Adults With Dementia in the US

Donovan T. Maust, MD, MS; Julie Strominger, MS; H. Myra Kim, ScD; Kenneth M. Langa, MD, PhD; Julie P. W. Bynum, MD, MPH; Chiang-Hua Chang, PhD; Helen C. Kales, MD; Kara Zivin, PhD; Erica Solway, PhD, MSW, MPH; Steven C. Marcus, PhD

IMPORTANCE Community-dwelling older adults with dementia have a high prevalence of psychotropic and opioid use. In these patients, central nervous system (CNS)–active polypharmacy may increase the risk for impaired cognition, fall-related injury, and death.

OBJECTIVE To determine the extent of CNS-active polypharmacy among community-dwelling older adults with dementia in the US.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional analysis of all community-dwelling older adults with dementia (identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis codes; N = 1 159 968) and traditional Medicare coverage from 2015 to 2017. Medication exposure was estimated using prescription fills between October 1, 2017, and December 31, 2018.

EXPOSURES Part D coverage during the observation year (January 1-December 31, 2018).

MAIN OUTCOMES AND MEASURES The primary outcome was the prevalence of CNS-active polypharmacy in 2018, defined as exposure to 3 or more medications for longer than 30 days consecutively from the following classes: antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, and opioids. Among those who met the criterion for polypharmacy, duration of exposure, number of distinct medications and classes prescribed, common class combinations, and the most commonly used CNS-active medications also were determined.

RESULTS The study included 1 159 968 older adults with dementia (median age, 83.0 years [interquartile range {IQR}, 77.0-88.6 years]; 65.2% were female), of whom 13.9% (n = 161 412) met the criterion for CNS-active polypharmacy (32 139 610 polypharmacy-days of exposure). Those with CNS-active polypharmacy had a median age of 79.4 years (IQR, 74.0-85.5 years) and 71.2% were female. Among those who met the criterion for CNS-active polypharmacy, the median number of polypharmacy-days was 193 (IQR, 88-315 polypharmacy-days). Of those with CNS-active polypharmacy, 57.8% were exposed for longer than 180 days and 6.8% for 365 days; 29.4% were exposed to 5 or more medications and 5.2% were exposed to 5 or more medication classes. Ninety-two percent of polypharmacy-days included an antidepressant, 47.1% included an antipsychotic, and 40.7% included a benzodiazepine. The most common medication class combination included an antidepressant, an antiepileptic, and an antipsychotic (12.9% of polypharmacy-days). Gabapentin was the most common medication and was associated with 33.0% of polypharmacy-days.

CONCLUSIONS AND RELEVANCE In this cross-sectional analysis of Medicare claims data, 13.9% of older adults with dementia in 2018 filled prescriptions consistent with CNS-active polypharmacy. The lack of information on prescribing indications limits judgments about clinical appropriateness of medication combinations for individual patients.

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Supplemental content

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Author Affiliations: Department of Psychiatry, University of Michigan, Ann Arbor (Maust, Zivin); Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Maust, Strominger, Kim, Langa, Zivin); Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor (Maust, Kim, Langa, Bynum, Chang, Zivin, Solway); Department of Internal Medicine, University of Michigan, Ann Arbor (Langa, Bynum, Chang); Institute for Social Research, University of Michigan, Ann Arbor (Langa); Department of Psychiatry, University of California–Davis, Sacramento (Kales); School of Social Policy and Practice, University of Pennsylvania, Philadelphia (Marcus).

Corresponding Author: Donovan T. Maust, MD, MS, Department of Psychiatry, University of Michigan, 2800 Plymouth Rd, NCRC 016-226W, Ann Arbor, MI 48109 (maustd@umich.edu).

The number of persons with dementia in the US is projected to grow to 50 million people by 2050,[1] but the US health care system is poorly equipped to deal with these patients and their complex medical and psychosocial needs.[2] Although memory impairment is the cardinal feature of dementia, behavioral and psychological symptoms (eg, apathy, delusions, agitation) are common during all stages of illness and cause significant caregiver distress.[3,4] Despite limited high-quality evidence of efficacy for pharmacological treatment,[5] clinicians regularly prescribe psychotropic medications to community-dwelling persons with dementia[6] in rates that far exceed use in the general older adult population.[7]

Central nervous system (CNS)–active polypharmacy (defined as combinations of multiple psychotropic or opioid medications or both psychotropic and opioid medications) has increased among older adults overall.[8] The potential for such prescribing may be particularly high among persons with dementia because medications accumulate in response to pervasive but transient behavioral symptoms. The Beers Criteria from the American Geriatrics Society advise against such polypharmacy given its association with increased fall risk.[9] These medications may also cause impaired cognition,[10] cardiac conduction abnormalities,[11] and respiratory suppression and death when involving opioids.[12] Given the high degree of comorbid medical illness and frailty among persons with dementia, associated risks from drug-drug and drug-disease interactions may be even greater than among older adults overall. In addition, persons with dementia may have difficulty articulating any adverse effects they are experiencing.

The limited data on CNS-active polypharmacy among persons with dementia are from Europe and do not include antiepileptic medications or opioids, thereby significantly underestimating the true extent of exposure to such combinations.[13-15] In light of pervasive psychotropic and opioid prescribing to persons with dementia in the US,[6] as well as the extent of CNS-active polypharmacy among older adults overall,[8] this analysis sought to determine the prevalence of polypharmacy among older adults with dementia living in the community, including the duration of exposure, the type of medication class combinations, and the most commonly prescribed individual medications.

Key Points

Question What is the prevalence of polypharmacy with central nervous system (CNS)–active medications among community-dwelling older adults with dementia in the US?

Findings In this cross-sectional analysis of 1 159 968 older adults with dementia, traditional Medicare, and prescription coverage in 2018, 13.9% were prescribed CNS-active polypharmacy, defined as overlapping prescription fills for 3 or more medications from the following drug classes: antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, and opioids.

Meaning In 2018, 13.9% of older adults with dementia in the US had filled prescriptions consistent with CNS-active polypharmacy.

Methods

The Michigan Medicine institutional review board approved this study. Informed consent was waived for this observational data analysis.

Cohort Identification

The study population included Medicare beneficiaries with continuous traditional fee-for-service (ie, Parts A and B but not Medicare Advantage) coverage between January 1, 2015, and December 31, 2017 (**Figure**).

The cohort was limited to those with at least 1 *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* dementia diagnosis code (eTable 1 in the Supplement) from a health care encounter that occurred from 2015 to 2017 using the inpatient (Medicare Provider Analysis and Review), carrier, and outpatient files; a period of 3 years was used for cohort identification to achieve greater sensitivity (0.80).[16]

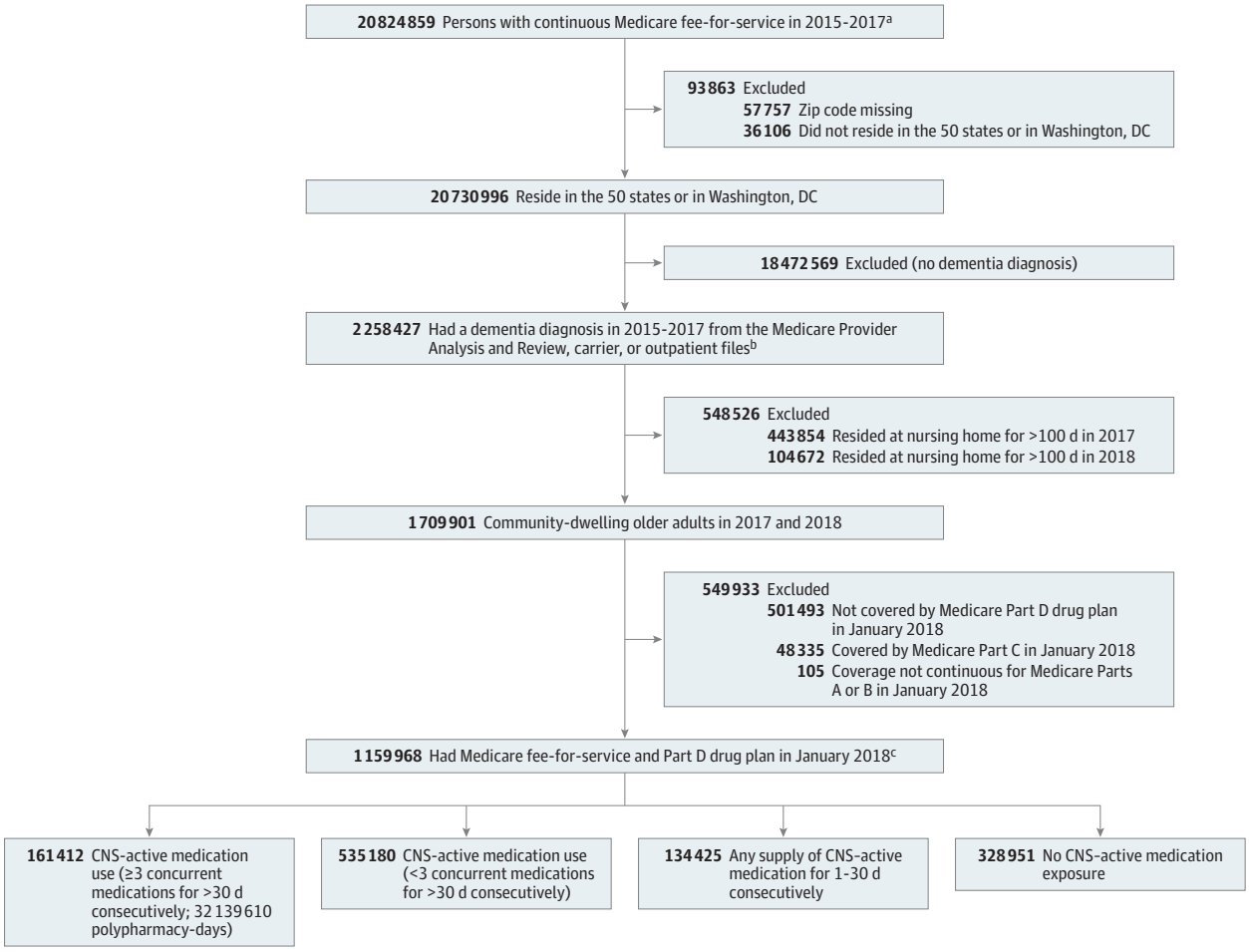
The outcome observation period was calendar year 2018. Because of the requirement of 3 years of Medicare coverage to identify dementia, cohort members were aged 68 years or older at the start of the 2018 observation year. To limit the analysis to community-dwelling beneficiaries, those who had been long-stay nursing home residents (ie, >100 days in long-term care[17]) in 2017 or 2018 were excluded. To be included in the final study cohort, beneficiaries with dementia were required to have Part D prescription drug coverage on January 1, 2018. The study cohort was followed up until the earliest of the censoring events (death, loss of Medicare fee-for-service coverage, enrollment in Medicare Advantage, or loss of Part D coverage) or the end of the observation year (December 31, 2018).

Polypharmacy Assessment and Outcomes

Based on the Beers Criteria from the American Geriatrics Society, the primary outcome was the prevalence of CNS-active polypharmacy in 2018 that was defined as concurrent exposure to 3 or more medications for longer than 30 days consecutively from the following 6 classes: antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, z-drugs), and opioids.[9] The Beers Criteria from 2015 did not include antiepileptics, but the updated Beers Criteria from 2019 did and were used for this analysis. Medications within each class were identified using the American Hospital Formulary Service (eTable 2 in the Supplement).

Medication exposure was estimated using prescription fills between October 1, 2017, and December 31, 2018 (ie, the observation year plus the 3 preceding months). Daily exposure to each CNS-active medication was determined using the fill date and days' supply; early fills (ie, October 1-December 31, 2017) were included to account for prescriptions received before the observation year began. Central nervous system-active polypharmacy was considered present

Figure. Study Population of Older Adults With Dementia for Assessment of Central Nervous System (CNS)–Active Polypharmacy



[a] From January 2015 to December 2017, persons had continuous Medicare Part A fee-for-service coverage (primarily covers inpatient and skilled nursing services) and Part B fee-for-service coverage (covers physician and outpatient services) but not Part C coverage (Medicare Advantage; beneficiaries enroll in a private health plan that delivers Medicare-covered Part A and Part B benefits).

[b] The Medicare Provider Analysis and Review file contains billing records (ie, claims) for inpatient care encounters (acute and skilled nursing). Outpatient encounters are captured in the carrier file (claims from noninstitutional clinicians such as physicians) and the outpatient file (claims for outpatient services from institutional clinicians, some of whom may also provide hospital services through Part A coverage).

[c] A sensitivity analysis also was conducted that removed the 182 150 who died during 2018; among the 977 818 survivors, 142 602 experienced CNS-active polypharmacy (29 888 544 polypharmacy-days). Medicare beneficiaries do not have to enroll in Part D (prescription drug coverage) but in this study those without it were excluded (see prior box).

when a beneficiary was simultaneously exposed to 3 or more CNS-active medications for longer than 30 days consecutively during the 2018 observation year. The medications did not have to be from different classes (eg, exposure to 3 antidepressants or exposure to 2 antipsychotics plus a benzodiazepine for >30 days consecutively; both combinations would meet the polypharmacy definition) per the Beers Criteria.

The cohort was split into 4 mutually exclusive groups based on exposure to CNS-active medications during the observation year: (1) 3 or more concurrent medications for longer than 30 days consecutively (met the criteria for a polypharmacy episode), (2) less than 3 concurrent medications for longer than 30 days consecutively, (3) any supply of medication for 1 to 30 days consecutively, and (4) no supply (no exposure). An episode of polypharmacy continued as long as 3 or more CNS-active medications were present, even if the constituent medications changed.

The polypharmacy-days of exposure formed the basis of the analysis. In addition to determining the overall prevalence, additional secondary outcomes included: (1) the total number of polypharmacy-days, (2) the number of distinct medications and distinct classes prescribed, (3) the most common combinations of CNS-active medication classes, and (4) the most-prescribed individual medications that contributed to polypharmacy.

Statistical Analysis

For descriptive purposes, baseline characteristics for the cohort overall and by CNS-active medication group were determined using demographic and clinical data derived from the

2017 Medicare Master Beneficiary Summary File, the Medicare Provider Analysis and Review files, carrier files (claims from noninstitutional clinicians such as physicians), and outpatient files (claims for outpatient services from institutional clinicians, some of whom may also provide hospital services through Part A coverage).

Race/ethnicity was included in the analysis given racial disparities in CNS-active prescribing[7] and was identified using the Research Triangle Institute race code variable available in the Medicare Master Beneficiary Summary File, which was developed by combining Social Security Administration data and beneficiary name and validated against beneficiary self-report in the Consumer Assessment of Healthcare Providers and Systems survey.[18]

Clinical characteristics included dementia type, overall comorbidity defined using the Elixhauser comorbidity index, and specific diagnoses potentially associated with CNS-active medication use, including mental health, insomnia, pain, and seizure diagnoses. Characteristics across CNS-active medication groups were compared using the Kruskal-Wallis test and the Mann-Whitney test for continuous variables (eg, age) and the χ^2 test for categorical variables (eg, depression).

Among those with CNS-active polypharmacy, the number of polypharmacy-days during the 2018 observation year were identified by summing the number of polypharmacy episodes for each person until the censoring event or end of the observation year, whichever came first. To address the possibility that the findings were related to medication use during end-of-life care, a sensitivity analysis was completed examining the primary outcomes with the cohort limited to those who survived through 2018.

This analysis was primarily descriptive and should be interpreted as exploratory. Limited statistical comparisons were completed to compare demographic and clinical characteristics across the 4 CNS-active polypharmacy exposure groups. The α level was set at .05 and the tests were 2-sided.

When reporting percentages related to CNS-active medication use (eg, percentage of polypharmacy-days involving ≥1 antidepressant), 95% CIs are not presented because the interval is not evident when reported to 1 significant figure after the decimal point. Data processing and analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

The study included 1 159 968 older adults with dementia; their median age was 83.0 years (interquartile range [IQR], 77.0-88.6 years) and 65.2% were female. In 2018, 28.4% were not exposed to any CNS-active medication; 11.6% were exposed to at least 1 CNS-active medication for 30 days consecutively or fewer; and 46.1% were exposed to at least 1 CNS-active medication for longer than 30 days consecutively but did not experience a CNS-active polypharmacy episode (**Table 1**). Central nervous system–active polypharmacy occurred in 13.9% (n = 161 412), yielding a total of 32 139 610 person-days of exposure (polypharmacy-days).

Characteristics of Those Who Met the Criterion for CNS-Active Polypharmacy

The persons exposed to polypharmacy were significantly younger (median age, 79.4 years [IQR, 74.0-85.5 years] vs 84.7 years [IQR, 78.8-89.9 years] in the no exposure group, $P < .001$) with larger percentages of non-Hispanic white (86.2% vs 76.7% in the no exposure group, $P < .001$) and low-income beneficiaries (36.2% vs 25.9% in the no exposure group, $P < .001$). In addition, the persons exposed to polypharmacy had a higher burden of medical comorbidity overall (median Elixhauser comorbidity score, 5 [IQR, 3-7] vs 3 [IQR, 1-5] in the no exposure group, $P < .001$). With the exception of cancer and cancer-related pain, the persons exposed to polypharmacy had a significantly higher prevalence of all individual clinical characteristics of interest, including noncancer pain, insomnia, psychiatric diagnoses, and seizure disorders ($P < .001$ for all).

Polypharmacy-Days, Medications, and Medication Classes for CNS-Active Polypharmacy

Of those who met the criterion for polypharmacy, the median number of polypharmacy-days was 193 (IQR, 88-315 polypharmacy-days). Of those with episodes of CNS-active polypharmacy, 57.8% were exposed for longer than 180 days and 6.8% for 365 days (**Table 2**). Of all polypharmacy-days, combinations with 3 CNS-active medications accounted for 55.3% of polypharmacy-days and 35.5% of exposed persons, 4 medications for 29.8% of polypharmacy-days and 35.1% of exposed persons, and 5 or more medications for 14.9% of polypharmacy-days and 29.4% of exposed persons. Combinations of medications from a single medication class accounted for 2.7% of polypharmacy-days and 1.8% of exposed persons; combinations of 3 classes, 48.3% of polypharmacy-days and 45.5% of exposed persons; 5 or more classes, 2.0% of polypharmacy-days and 5.2% of exposed persons.

Most Common Combinations and Medications for CNS-Active Polypharmacy

Of the medication classes associated with CNS-active polypharmacy, antidepressants accounted for 92.0% of polypharmacy-days, followed by antiepileptics (62.1%), antipsychotics (47.1%), benzodiazepines (40.7%), opioids (32.3%), and z-drugs (6.0%; **Table 3**). For polypharmacy combinations including the 5 nonantidepressant classes, antidepressants were the most commonly co-prescribed class. An opioid was co-prescribed with an antiepileptic for 19.8% of polypharmacy-days, with an antipsychotic for 9.1% of polypharmacy-days, with a benzodiazepine for 13.1% of polypharmacy-days, or with another opioid for 5.1% of polypharmacy-days.

The most common CNS-polypharmacy class combination included at least 1 antidepressant, 1 antiepileptic, and 1 antipsychotic, accounting for 12.9% of polypharmacy-days (eTable 3 in the Supplement). Among the 20 most frequent class combinations, 17 included an antidepressant and 12 included an antiepileptic. Antipsychotics and benzodiazepines were each part of 10 of the 20 most frequent combinations; opioids were part of 9 of the top 20. An opioid was prescribed with at least 1 CNS depressant in 8 of the 20 most

Table 1. Cohort Characteristics by Exposure to Central Nervous System (CNS)–Active Medications and Overall

Characteristic	Exposure to CNS-active medications during 2018 observation year				
	≥3 concurrent medications for >30 d consecutively (polypharmacy)	<3 concurrent medications for >30 d consecutively	Any supply of medication for 1-30 d consecutively	No exposure	Overall
Community-dwelling older adults with dementia in 2018, No. (%)	161 412 (13.9)	535 180 (46.1)	134 425 (11.6)	328 951 (28.4)	1 159 968 (100)
Sex, No. (%)					
Female	114 920 (71.2)	359 909 (67.3)	82 132 (61.1)	198 992 (60.5)	755 953 (65.2)
Male	46 492 (28.8)	175 271 (32.7)	52 293 (38.9)	129 959 (39.5)	404 015 (34.8)
Age group, median (IQR), y	79.4 (74.0-85.5)	82.9 (77.1-88.4)	83.7 (77.8-89.2)	84.7 (78.8-89.9)	83.0 (77.0-88.6)
68-69	12 231 (7.6)	19 889 (3.7)	4408 (3.3)	8912 (2.7)	45 440 (3.9)
70-74	35 715 (22.1)	72 876 (13.6)	16 574 (12.3)	34 317 (10.4)	159 482 (13.7)
75-79	36 946 (22.9)	105 205 (19.7)	24 313 (18.1)	54 348 (16.5)	220 812 (19.0)
80-84	32 937 (20.4)	121 669 (22.7)	29 978 (22.3)	72 363 (22.0)	256 947 (22.2)
85-89	26 079 (16.2)	118 373 (22.1)	30 391 (22.6)	78 958 (24.0)	253 801 (21.9)
90-94	13 724 (8.5)	72 722 (13.6)	20 516 (15.3)	55 936 (17.0)	162 898 (14.0)
≥95	3780 (2.3)	24 446 (4.6)	8245 (6.1)	24 117 (7.3)	60 588 (5.2)
Race/ethnicity, No. (%)[a]					
Non-Hispanic White	138 465 (86.2)	440 899 (82.7)	104 666 (78.2)	251 368 (76.7)	935 398 (81.0)
Non-Hispanic Black	8123 (5.1)	37 933 (7.1)	13 617 (10.2)	34 387 (10.5)	94 060 (8.1)
Hispanic	10 007 (6.2)	33 300 (6.3)	9263 (6.9)	21 381 (6.5)	73 951 (6.4)
Other	4022 (2.5)	20 817 (3.9)	6352 (4.7)	20 513 (6.3)	51 704 (4.5)
Low-income subsidy status, No. (%)[b]	58 381 (36.2)	147 672 (27.6)	36 913 (27.5)	85 271 (25.9)	328 237 (28.3)
Rurality, No. (%)[c]					
Urban	138 651 (86.0)	458 654 (85.8)	114 440 (85.2)	283 468 (86.2)	995 213 (85.8)
Rural	22 669 (14.1)	76 197 (14.3)	19 916 (14.8)	45 307 (13.8)	164 089 (14.2)
Dementia type, No. (%)					
Alzheimer	65 730 (40.7)	220 917 (41.3)	48 870 (36.4)	124 990 (38.0)	460 507 (39.7)
Vascular	28 971 (17.9)	81 860 (15.3)	17 935 (13.3)	40 889 (12.4)	169 655 (14.6)
With Lewy bodies	7065 (4.4)	16 906 (3.2)	3186 (2.4)	6719 (2.0)	33 876 (2.9)
Frontotemporal	3640 (2.3)	9480 (1.8)	1854 (1.4)	4268 (1.3)	19 242 (1.7)
Unspecified[d]	75 602 (46.8)	256 492 (47.9)	72 582 (54.0)	174 041 (52.9)	578 717 (49.9)

(continued)

Table 1. Cohort Characteristics by Exposure to Central Nervous System (CNS)–Active Medications and Overall (continued)

Characteristic	Exposure to CNS-active medications during 2018 observation year				
	≥3 concurrent medications for >30 d consecutively (polypharmacy)	<3 concurrent medications for >30 d consecutively	Any supply of medication for 1-30 d consecutively	No exposure	Overall
Comorbidities[e]					
Elixhauser comorbidity score, median (IQR)[f]	5 (3-7)	4 (2-6)	4 (2-6)	3 (1-5)	4 (2-6)
Noncancer pain	138 123 (85.6)	407 518 (76.1)	101 050 (75.2)	204 954 (62.3)	851 645 (73.4)
Arthritis	87 751 (54.4)	216 065 (40.4)	54 705 (40.7)	90 896 (27.6)	449 417 (38.7)
Back pain	71 933 (44.6)	159 720 (29.8)	38 141 (28.4)	55 932 (17.0)	325 726 (28.1)
Neuropathic pain	30 219 (18.7)	66 579 (12.4)	14 052 (10.5)	22 220 (6.8)	133 070 (11.5)
Headache	12 719 (7.9)	25 829 (4.8)	5824 (4.3)	7943 (2.4)	52 315 (4.5)
Fibromyalgia	12 173 (7.5)	16 398 (3.1)	3168 (2.4)	4026 (1.2)	35 765 (3.1)
Migraine headache	4824 (3.0)	6377 (1.2)	1132 (0.8)	1357 (0.4)	13 690 (1.2)
Psychogenic	511 (0.3)	316 (0.1)	56 (<0.1)	57 (<0.1)	940 (0.1)
Depression	77 658 (48.1)	144 351 (27.0)	17 343 (12.9)	19 734 (6.0)	259 086 (22.3)
Anxiety	71 510 (44.3)	123 680 (23.1)	19 709 (14.7)	23 507 (7.1)	238 406 (20.6)
Cancer	21 011 (13.0)	76 783 (14.3)	23 261 (17.3)	45 528 (13.8)	166 583 (14.4)
Cancer-related pain	327 (0.2)	576 (0.1)	279 (0.2)	266 (0.1)	1448 (0.1)
Insomnia	24 134 (15.0)	39 154 (7.3)	7056 (5.2)	8293 (2.5)	78 637 (6.8)
Seizure disorder	15 217 (9.4)	23 803 (4.4)	3110 (2.3)	3510 (1.1)	45 640 (3.9)
Bipolar disorder	13 474 (8.3)	8852 (1.7)	1112 (0.8)	1169 (0.4)	24 607 (2.1)
Schizophrenia or schizoaffective disorder	7492 (4.6)	6756 (1.3)	814 (0.6)	986 (0.3)	16 048 (1.4)
Other psychotic disorder	8697 (5.4)	11 144 (2.1)	1936 (1.4)	2643 (0.8)	24 420 (2.1)
Substance use disorder					
Alcohol	4129 (2.6)	8225 (1.5)	1948 (1.4)	3674 (1.1)	17 976 (1.5)
Drugs other than alcohol	6856 (4.2)	5544 (1.0)	1031 (0.8)	920 (0.3)	14 351 (1.2)

Abbreviation: IQR, interquartile range.

[a] Classified using the Research Triangle Institute race variable. Of the overall cohort, 4855 (0.4%) were missing race/ethnicity. The percentages were calculated using denominators after excluding those with missing race.

[b] Considered present if a given beneficiary was eligible for or enrolled in the Part D low-income subsidy for at least 1 month during the observation period.

[c] Derived using beneficiary zip code and rural-urban commuting area codes. Urban areas comprise urban core and suburban areas; rural areas comprise large town, small town, and isolated rural areas. Of the overall cohort, 666 (0.1%) were missing rurality. The percentages were calculated using denominators after excluding those with missing rurality.

[d] Did not receive 1 of the otherwise specified dementia diagnoses. The dementia subtypes were not mutually exclusive.

[e] Data are expressed as No. (%) unless otherwise indicated. A comorbidity was considered present if a diagnosis indicating the given condition was present on at least 1 inpatient or 2 or more outpatient encounters on 2 separate days during 2017. Diagnosis codes for each comorbidity appear in eTable 1 in the Supplement.

[f] Measures patient disease burden based on administrative data (range, 0-30; a score of 4 indicates the presence of 4 comorbidities based on claims data).

Table 2. Central Nervous System (CNS)–Active Polypharmacy-Days, Number of Medications, and Number of Medication Classes Among Community-Dwelling Older Adults With Dementia in 2018

	No. (%)	
	Exposure, polypharmacy-days (n = 32 139 610)[a]	Exposed persons (n = 161 412)[b]
CNS-active polypharmacy-days		
31-180	6 081 538 (18.9)	68 156 (42.2)
181-270	6 292 042 (19.6)	29 978 (18.6)
271-364	15 737 525 (49.0)	52 241 (32.4)
365	4 028 505 (12.5)	11 037 (6.8)
No. of unique CNS-active medications		
3	17 767 425 (55.3)	57 253 (35.5)
4	9 580 013 (29.8)	56 656 (35.1)
5	3 443 810 (10.7)	29 954 (18.6)
≥6	1 348 362 (4.2)	17 549 (10.9)
No. of unique CNS-active medication classes[c]		
1	857 492 (2.7)	2969 (1.8)
2	10 538 694 (32.8)	37 082 (23.0)
3	15 512 267 (48.3)	73 443 (45.5)
4	4 597 057 (14.3)	39 519 (24.5)
≥5	634 100 (2.0)	8399 (5.2)

[a] Defined as exposure to 3 or more CNS-active medications for longer than 30 days consecutively from the following classes: antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, and opioids.

[b] Each person was assigned to a mutually exclusive group based on the maximum number of overlapping medications or classes during a polypharmacy episode.

[c] Assigned using the American Hospital Formulary Service, which may not reflect the prescribing indication (eg, quetiapine is captured as an antipsychotic even though it may be prescribed for insomnia or anxiety).

Table 3. Medication Classes and Class Combinations Contributing to Central Nervous System (CNS)–Active Polypharmacy Among Community-Dwelling Older Adults With Dementia in 2018

Additional medication class	Overall	Medication class, % CNS-active polypharmacy-days (n = 32 139 610)[a]					
		Antidepressant	Antiepileptic	Antipsychotic	Benzodiazepine	Opioid	Z-drug[b]
Antidepressant	92.0	46.6	55.3	42.7	36.4	28.7	5.1
Antiepileptic	62.1		14.6	25.2	20.7	19.8	3.2
Antipsychotic	47.1			5.3	17.8	9.1	1.8
Benzodiazepine	40.7				2.1	13.1	2.5
Opioid	32.3					5.1	2.4
Z-drug[b]	6.0						<0.1

[a] The percentages involve both the column and row for the medication classes (eg, where antidepressants and antiepileptics meet, the percentage represents CNS-active polypharmacy-days involving both an antidepressant and an antiepileptic). For cells where the row and column headings are the same (eg, antidepressants), the percentage represents CNS-active polypharmacy-days involving 2 or more medications from that class. Medication class was assigned using the American Hospital Formulary Service, which may not reflect the prescribing indication (eg, quetiapine is captured as an antipsychotic even though it may be prescribed for insomnia or anxiety).

[b] Defined as nonbenzodiazepine benzodiazepine receptor agonist hypnotics.

frequent combinations: specifically, with an antiepileptic in 5, a benzodiazepine in 5, and an antipsychotic in 4.

Gabapentin was the individual medication that accounted for the largest percentage of polypharmacy-days (33.0%; **Table 4**) and accounted for 53.2% of all antiepileptic polypharmacy-days. The next most-prescribed medications were trazodone (26.0%) and quetiapine (24.4%). The remaining medications among the top 10 spots were antidepressants (mirtazapine [19.9%], sertraline [18.7%], escitalopram [14.7%], and duloxetine [14.5%]) and benzodiazepines (lorazepam [12.9%], clonazepam [12.0%], and alprazolam [12.0%]). The most common opioids were hydrocodone (11.5%) and tramadol (9.2%).

Sensitivity Analysis

The prevalence of CNS-active polypharmacy among those who did not die during the 2018 observation year (n = 977 818) was slightly higher (14.6%) than among the cohort overall. Of those who met the criterion for polypharmacy in the sensitivity cohort, the median number of polypharmacy-days was 214 (IQR, 94-326 polypharmacy-days). Among those who were exposed to CNS-active medications, 57.6% were exposed for longer than 180 days and 7.7% were exposed for the entire year (eTable 4 in the Supplement). Combinations with 3 CNS-active medications accounted for 55.2% of polypharmacy-days, 4 medications for 29.8% of polypharmacy-days, and 5 or more medications for 15.0% of polypharmacy-days. Of all polypharmacy-days, 2.7% occurred with patients prescribed 3 medications from a single CNS-active class and 48.1% were accounted for by 3 medication classes.

Discussion

In this large Medicare sample of all community-dwelling older adults with dementia and Part D prescription drug coverage,

Table 4. Twenty Medications Most Frequently Contributing to Central Nervous System (CNS)–Active Polypharmacy Among Community-Dwelling Older Adults With Dementia in 2018

Rank	Generic name	Polypharmacy-days, % (n = 32 139 610)[a]	Persons, % (n = 161 412)[b]	Class[c]	Mechanism[19]
1	Gabapentin	33.0	36.7	Antiepileptic	γ-aminobutyric acid analogue
2	Trazodone	26.0	28.9	Antidepressant	Inhibits serotonin reuptake; histamine and α1-adrenergic antagonist
3	Quetiapine	24.4	27.1	Antipsychotic	Dopamine, serotonin, histamine, and α1-adrenergic receptor antagonist
4	Mirtazapine	19.9	22.0	Antidepressant	α_2-adrenergic and histamine antagonist; inhibits serotonin reuptake
5	Sertraline	18.7	21.1	Antidepressant	Serotonin reuptake inhibitor
6	Escitalopram	14.7	16.9	Antidepressant	Serotonin reuptake inhibitor
7	Duloxetine	14.5	15.6	Antidepressant	Serotonin and norepinephrine reuptake inhibitor
8	Lorazepam	12.9	19.1	Benzodiazepine	Enhances γ-aminobutyric acid activity
9	Clonazepam	12.0	13.6	Benzodiazepine	Enhances γ-aminobutyric acid activity
10	Alprazolam	12.0	16.3	Benzodiazepine	Enhances γ-aminobutyric acid activity
11	Citalopram	11.7	13.1	Antidepressant	Serotonin reuptake inhibitor
12	Divalproex[d]	11.7	12.7	Antiepileptic	Increases concentrations of γ-aminobutyric acid
13	Hydrocodone[e]	11.5	20.1	Opioid	μ-opiate agonist
14	Bupropion	10.6	11.1	Antidepressant	Norepinephrine and dopamine reuptake inhibitor
15	Risperidone	9.4	10.9	Antipsychotic	Dopamine and serotonin receptor antagonist
16	Tramadol	9.2	18.2	Opioid	μ-opiate agonist; serotonin and norepinephrine reuptake inhibitor
17	Oxycodone[f]	8.4	12.6	Opioid	μ-opiate agonist
18	Levetiracetam	8.1	8.0	Antiepileptic	Antiepileptic mechanism unclear[20]
19	Venlafaxine	8.0	8.2	Antidepressant	Serotonin and norepinephrine reuptake inhibitor
20	Olanzapine	7.7	8.4	Antipsychotic	Dopamine, serotonin, histamine, and α1-adrenergic receptor antagonist

[a] Percentages sum to greater than 100 because a given beneficiary may take 3 or more medications each polypharmacy-day.

[b] Limited to those who experienced an episode of CNS-active polypharmacy (defined as >30 days consecutively with concurrent exposure to ≥3 medications from the following 6 classes: antidepressants, antiepileptics, antipsychotics, benzodiazepines, opioids, and nonbenzodiazepine benzodiazepine receptor agonist hypnotics).

[c] Assigned using the American Hospital Formulary Service, which may not reflect the prescribing indication (eg, quetiapine is captured as an antipsychotic even though it may be prescribed for insomnia or anxiety).

[d] Divalproex, valproate, or valproic acid.

[e] Includes combination medications (eg, hydrocodone/acetaminophen).

[f] Includes combination medications (eg, oxycodone/acetaminophen).

13.9% were exposed to CNS-active polypharmacy in 2018, defined as exposure to 3 or more medications (antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, and opioids) for longer than 30 days consecutively. Of those prescribed such a regimen, 57.8% were exposed for longer than 180 days and 6.8% for a full year. Antidepressants were the most common constituent medication class. The most common medications associated with CNS-active polypharmacy included an antiepileptic (gabapentin), an antidepressant (trazodone), and an antipsychotic (quetiapine).

To our knowledge, there are no prior studies among noninstitutionalized adults with dementia in the US with which to compare these results. Two analyses among older adults in the US overall (not limited to those with dementia) found that less than 1.5% took 3 or more CNS-active medications; both studies included opioid medications but not antiepileptics.[8,21] However, international studies of polypharmacy have not included either. In international studies specifically among adults with dementia, the prevalence of psychotropic polypharmacy ranged from 13.8% to 50% across studies that used varying definitions of polypharmacy (ie, 2 vs 3 medications with different overlapping criteria) and included those receiving long-term care.[13-15,22-24] Although this analysis excluded persons receiving federally regulated long-term care, Medicare beneficiaries in assisted living settings in the community were included because there is not a reliable way to identify them from Medicare claims; therefore, these persons may be overrepresented among those exposed to polypharmacy.[25]

This analysis used a relatively conservative definition of polypharmacy that required more than 30 days of overlap for at least 3 medications. A 30-day supply of a CNS-active medication that was either meant for short-term use or discontinued due to adverse effects would not contribute to polypharmacy—to do so, that medication (and ≥2 others) would have required refills to cross the polypharmacy threshold of longer than 30 days, suggesting ongoing therapy. Had a more conservative threshold been used, there still would have been a significant burden of polypharmacy: 77.7% of the polypharmacy sample was exposed for longer than 3 months (>90 days). In addition to relatively long periods, the number of medications frequently exceeded the Beers Criteria threshold in that 35.1% of those exposed to polypharmacy received 4 medications and 29.4% received 5 or more.

Antidepressants were the most common constituent medication class, consistent with their place as the psychotropic class most commonly prescribed both to older adults overall and those with dementia.[6,7] There is minimal high-quality evidence to support the efficacy of antidepressants to treat depression in patients with dementia.[26] Antidepressants may be

prescribed for a variety of other indications based on varying levels of evidence; for example, to treat agitation, a use supported by the Citalopram for Agitation in Alzheimer Disease Study (CitAD) trial,[11] or to treat apathy, which resembles depression and is distressing to family but does not benefit from use of antidepressants.[27,28] Additional potential indications are pain or insomnia and these diagnoses were higher among those experiencing polypharmacy. Trazodone and mirtazapine, which are the top 2 antidepressants that contributed to polypharmacy-days, are both commonly prescribed off-label for insomnia.[29,30]

As with antidepressants, other medications that contributed to polypharmacy may have been prescribed for multiple indications, including gabapentin and quetiapine, which are among the top individual medications. Even though gabapentin is captured by the Beers Criteria as an antiepileptic, and seizure disorders were more common among those exposed to polypharmacy, the majority of its use has been found to be for off-label psychiatric or pain disorders.[31] Similarly, quetiapine is an antipsychotic but it is frequently prescribed off-label for anxiety or insomnia.[32]

Apart from cancer and cancer-related pain, the prevalence of all other clinical conditions including insomnia, mental disorders, and noncancer pain was higher among those with CNS-active polypharmacy. However, it is not possible to directly link the medications prescribed to their multiple potential indications.

There are several specific risks related to CNS-active polypharmacy and the constituent medications. First, there is a risk of respiratory suppression and death from combinations of opioids and CNS depressants or drugs termed *opioid potentiators*, including benzodiazepines, antipsychotics, and gabapentinoids, which are subject to a black-box warning from the US Food and Drug Administration.[33] In this analysis, 41% of opioid polypharmacy-days included a benzodiazepine and 28% included an antipsychotic.

Second, several antipsychotics and citalopram cause QT-interval prolongation, which increases the risk for cardiac arrhythmia.[11,34] Third, fall-related injury is associated with many CNS-active medications, both individually and in combination,[21,35,36] and this increased fall risk associated with CNS-active polypharmacy is the reason it was added to the Beers Criteria as potentially inappropriate.[37]

Fourth, many of these medications adversely affect cognition, an undesired side effect in those who have received a dementia diagnosis, a diagnosis applied in clinical practice to patients who have experienced significant declines in cognition and function. Among older adults with dementia in the Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease trial, patients who received an antipsychotic experienced a score decline on the Mini-Mental State Examination that was nearly 2.5 points (on a 30-point scale) higher than among those treated with placebo over 36 weeks of treatment.[38] Benzodiazepines also impair cognition, with more pronounced effects among older patients.[39] In the CitAD trial of citalopram for agitation in dementia,[11] those receiving citalopram experienced worsening of cognition relative to those receiving placebo. In addition to class-specific effects, additional burden of CNS-active polypharmacy overall has been associated with additional cognitive decline.[10]

Limitations

This study has several limitations. First, the prescription medication claims may have overestimated the actual exposure to polypharmacy if the prescriptions were filled but not taken or only taken on an as-needed basis.

Second, without knowing the indication for the medications or examining the range of prescribed dosages, it is not possible to assess the appropriateness of the particular combinations used. Third, the specific harms associated with CNS-active polypharmacy in this cohort were not examined.

Fourth, to limit the cohort to those with dementia, the analysis was limited to those with traditional fee-for-service Medicare and Part D prescription coverage, which limits generalizability to all older adults. Fifth, cohort identification relied on a dementia diagnosis in Medicare claims data, which may mean some individuals with dementia ended up being excluded, whereas others who had been identified did not have the illness. However, 3 years of data were used to maximize sensitivity of the algorithm to identify those with dementia.[16] Sixth, these data did not provide information on dementia severity.

Conclusions

In this cross-sectional analysis of Medicare claims data, 13.9% of older adults with dementia in 2018 filled prescriptions consistent with CNS-active polypharmacy. The lack of information on prescribing indications limits judgments about clinical appropriateness of medication combinations for individual patients.

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Concept and design: Maust, Strominger, Kim, Bynum, Kales, Solway, Marcus.
Acquisition, analysis, or interpretation of data: Maust, Strominger, Kim, Langa, Bynum, Chang, Zivin.
Drafting of the manuscript: Maust, Strominger, Marcus.
Critical revision of the manuscript for important intellectual content: Maust, Kim, Langa, Bynum, Chang, Kales, Zivin, Solway, Marcus.
Statistical analysis: Maust, Strominger, Chang, Marcus.
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