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Central Nervous System Medication Burden and Serious Falls in Older Nursing Home Residents

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Abstract

Objectives—To examine the association between CNS medication burden and serious falls in those with a recent fall history.

Design—Nested-case control study; cases matched to four controls by age, gender, and date.

Setting—US nursing homes

Participants—5,556 residents age ≥ 65 with a recent fall history admitted to a nursing home between 1/1–9/30/2010 and followed until discharge, death, or 12/31/2010.

Measurements—Outcome was serious falls as per Medicare Part A and B ICD/CPT codes. CNS burden, from Medicare Part D data, was calculated by dividing the daily dose of each CNS agent (i.e., specific antidepressants, antiepileptic, antipsychotic, benzodiazepine and opioid receptor agonists) received during the six days prior to the index (outcome) date by the minimum effective geriatric daily dose and summing the results across medications.

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Results—There were 367 cases and 1468 matched controls. Those taking 3+ CNS standardized daily doses were more likely to have a serious fall than those not taking any CNS medications (Adjusted Odds Ratio 1.83; 95% confidence interval 1.35–2.48). There was no significant difference in fall risk for residents taking >0 to <3 CNS standardized daily doses compared to residents taking no CNS medications (Adjusted Odds Ratio 0.85; 95% CI 0.63–1.15).

Conclusion—CNS medication burden, approximately 3+ standardized daily doses, was associated with an increased risk of serious falls in nursing home residents with recent fall. Clinicians should be vigilant for opportunities to discontinue or decrease the doses of individual CNS medications and/or consider non-pharmacological alternatives. Such interventions that reduce use of CNS medications in nursing homes could reduce fall rates but further research is needed to confirm this.

Keywords

aged; nursing homes; falls; psychoactive medications

INTRODUCTION

A major quality and safety concern for older nursing home residents is that at least 50% will have new falls.^{1–3} In particular, 5–10% of new falls are sufficiently serious to require emergency room care or hospitalization.^{1–4} These risks are even higher in those with a fall history in the previous year and this condition is included in the current American Geriatrics Society Beers drug-disease/condition interaction criteria.^{1–4}

One potentially ameliorable risk factor for serious falls in older nursing home residents with a history of falls is the use of medications that affect the central nervous system (CNS), including certain antidepressants, antiepileptics, antipsychotics, benzodiazepine receptor agonists, and opioid receptor agonists.^{5–7} A purported mechanism common to these CNS medications is sedation which can lead to a slowing of reaction time and impaired balance.^{5–7} Not surprisingly, fall risk is likely to be even higher in those taking multiple CNS medications.^{8–10} However, few studies have examined this association or dose-response-relationships in older nursing home residents.^{11,12} This is important as removing CNS medications might not be advisable for many residents with a history of falls because they need these drugs for specific conditions. However, risk might be averted by using non-pharmacological treatments and/or a reduction in CNS medication dosing.

Thus, there is an important knowledge gap regarding a potential threshold above which the burden of CNS medications may result in a meaningful increased risk of serious falls. Further, nursing home residents are at far greater risk for injurious falls than community dwelling elderly. Therefore, the objective of the present study was to examine the association between CNS medication dosage burden, as quantified by their combined standardized daily dose (SDD), and the risk of serious falls in older nursing home residents with a recent fall history.

METHODS

Study Design, and Source of Data

We used a nested case-control design and national data for older nursing home residents with a history of falls. We used Minimum Data Set (MDS) information merged with 2009–2010 Medicare claims and Prescription Drug Event (PDE) data from the Centers for Medicare and Medicaid Services (CMS) for a random 10% sample of fee-for-service beneficiaries continuously enrolled in Medicare Parts A, B, and D, obtained under a data use agreement between the University of Pittsburgh investigators and CMS. The MDS is a comprehensive assessment and screening tool completed at nursing home admission and every 90 days thereafter, or after an acute change in medical status.^{13–15} The MDS contains information from over 300 questions regarding resident demographics, physical and psychosocial function, and medical diagnoses.^{13–15} The MDS has excellent reliability and validity.^{13–16} We also utilized Medicare MedPAR files (inpatient/skilled nursing facility claims) and the outpatient facility and physician billing (i.e., carrier) claims to extract International Classification of Diseases (ICD-9)/Current Procedural Terminology (CPT) codes from hospital, outpatient, and long-term care settings.¹⁶ Finally, we used Medicare Part D PDE data, which contains information such as the date of prescription fill, National Drug Code (NDC) number, and number of days' supply dispensed.¹⁴ This study was approved and consent waived by the University of Pittsburgh Institutional Review Board.

Sample

The sample was derived using MDS v2.0 assessment records over 1/1/2010–9/30/2010. Because prescription drugs used during skilled nursing facility (SNF) stays are rolled into Medicare Part A charges, and Part D medication benefits only cover prescriptions dispensed during non-skilled portions of long-term care stays, we excluded nursing home stays or portions of stays that were covered by Medicare Part A. Specifically, we used a combination of the MDS reason for assessment fields (AA8A, AA8B), MDS admission and discharge dates, and SNF claims to identify and exclude entire stays or portions of stays that were for skilled care and covered by Part A. Residents were followed from the first day of the non-skilled nursing stay episode until discharge, death, or 12/31/2010. For those residents who stayed in the nursing home beyond 9/30/2010, MDS v3.0 discharge records were used to identify if the residents were discharged by 12/31/2010. The sample was restricted to those residents 65 years of age or older with a history of a fall and/or hip fracture in the previous year using ICD-9 diagnosis (E880–888, 820), ICD-9 procedure codes (7855, 7905, 7915, 7925, 7935, 7965), or CPT codes (27227, 27228, 27230, 27232, 27234–27236, 27238, 27240, 27242, 27244–27246, 27248) from emergency room visits and/or hospitalizations in Medicare Part A and B claim files and/or MDS assessments that coded yes to one of three questions: as falling within past 30 days or a fall within the past 31–180 days or a hip fracture within the past 180 days (fields J4a-c).^{13,17–21} We further excluded hospice/palliative care residents and residents with non-skilled nursing home stays lasting fewer than 7 days. This final sample of older nursing home residents with a history of any fall or hip fracture consisted of 5,556 nursing home episodes, including 2,703 admissions that began as non-SNF stays and 2,853 stays that started as Part A-covered SNF stays but later converted to non-skilled stays not covered by Part A.

Cases and Controls

Both cases and controls were drawn from the sample of 5,556 nursing home episodes described above. Cases were defined as individuals with falls ICD-9 diagnosis codes and/or hip fractures ICD-9 diagnosis/procedure codes or CPT codes as indicated above resulting in an emergency room visit and/or hospitalization during the nursing home stay.^{17–21} We chose to focus on serious falls as they are more clinically important and lead to an overall evaluation of the resident. The ICD-9 diagnosis and CPT codes for falls and hip fractures are consistent with those used by the National Committee for Quality Assurance (NCQA) in their Potentially Harmful Drug-Disease Interactions in the Elderly (Table DDE-A) quality measure.²² This approach for hip fractures has shown to be accurate and sensitive as compared to medical record review.^{20,21} Each case was matched with 4 controls based on age (birth dates within 1 year), gender, and date of case event (i.e., outcome of serious falls). For example, a case (hip fracture on 9/1/2009) was identified as an 83 year old man. We would randomly select from the hitherto unmatched controls, four other males whose age could range from 82–84 and was a nursing home resident on 9/1/2009.

Exposure

CNS medication use, determined from Part D PDE data, was operationally defined as the receipt of medications within 6 days prior to the outcome date from any of the following five classes: 1) tricyclic (TCA), selective serotonin reuptake inhibitor (SSRI), or serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants; 2) antiepileptics; 3) antipsychotics; 4) benzodiazepine receptor agonist hypnotics, and 5) opioid receptor agonists.²³ We chose the exposure window of 6 days to make sure that any new CNS medication with an average half-life of 24–36 hours would be at steady state (4 half-lives) the day before the outcome was measured. The rationale for combining the use of CNS medications is that previous studies have shown them to have similar risk profiles.^{5–12} CNS medications started on the day of index (outcome) date were excluded as some of them could have been used for the treatment of a serious fall. Also of note, benzodiazepines (with the exception of non-benzodiazepine, benzodiazepine receptor agonist hypnotics such as zolpidem) were not included since they were not covered by Medicare Part D until 2012. We used the Medispan® Electronic Drug File v2 (Wolters Kluwer Health, Inc., Indianapolis, IN) to identify NDCs for individual CNS agents. We then created an independent variable for CNS burden using the previously validated calculation:

$$\text{CNS SDD} = \frac{\text{CNS Drug}_1}{\text{MEGDD}_1} + \frac{\text{CNS Drug}_2}{\text{MEGDD}_2} + \dots + \frac{\text{CNS Drug}_k}{\text{MEGDD}_k},$$

where “CNS drug” is the resident’s actual daily dose and “MEGDD” is the minimum effective geriatric daily dose as reported in a commonly used geriatric pharmacotherapy source (Supplementary Appendix S1).^{23,24} An exception was that for opioid receptor agonists, we converted the resident’s actual daily dose by multiplying by its conversion factor to an oral morphine equivalent using values from a recent consensus review (Supplementary Appendix S2).²⁵ The “MEGDD” for opioid receptor agonists was 10 mg of oral morphine sulfate.^{23,24} A “CNS Drug” is divided by its “MEGDD,” which is then added

with other likewise calculated values from any additional CNS medications used. Based on a previously published approach and the distribution of the data, we created a categorical variable for CNS SDD (0, >0 – <3, and 3+).²³ For descriptive purposes only, we also calculated the number of CNS drugs used, mean SDD, and interquartile range for the five individual CNS medication classes.

Covariates

We also considered other risk factors for serious falls.^{3, 26} As of the index date of admission, demographics were derived from the MDS for race/ethnicity (white non-Hispanic, or other). Regarding health status factors, from the most recent MDS assessment, we determined residents' cognitive function using the Cognitive Performance Scale (CPS); we categorized cognitive function as intact (scores of 0 or 1), mild to moderate impairment (scores of 2, 3, or 4), and severe impairment (scores of 5 or 6).²⁷ Sensitivity and specificity for the CPS in detecting residents with cognitive impairment are similar to that of the Mini-Mental State Exam.²⁷ We also used variables from MDS data for use of a walking aid, vision impairment, wandering, and urinary incontinence.^{3, 26} MDS data and ICD-9 codes were used to create a variable for Parkinson's disease. Using ICD-9 codes from the 12 months prior to the index date, we created a variable for the Charlson Comorbidity Index, excluding dementia, based on the method of Deyo et al.²⁸ Using Part D data, we created a variable for use of other medications that may increase the risk of falls/fractures/syncope (i.e., other non TCA/SSRI/SNRI antidepressants, peripheral alpha blockers [e.g., prazosin], and skeletal muscle relaxants), and the total number of drugs after excluding CNS medications, other antidepressants, peripheral alpha blockers, and skeletal muscle relaxants at admission date.^{6, 29, 30}

Besides these demographic and health status factors, we also created variables for CNS medication indications using MDS, and Part A and B data. These included anxiety disorder, depression (Depression Rating Scale [DRS] scores >3), seizure disorder, moderate/severe bodily pain, and use of acetylcholinesterase inhibitor as a marker for dementia.³¹

Statistical Analyses

We used descriptive statistics to summarize characteristics of cases and controls and the exposure measures overall and separately for each class. We compared resident characteristics using conditional (to account for matching) logistic regression models.³² For the main analyses, we used a series of conditional logistic regression models with serious falls as the dependent variable and CNS SDD as the primary independent variable.³² We included the above mentioned covariates (except matching variables) as additional independent variables. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were used to draw main conclusions. We also conducted sensitivity analyses which included all independent variables from the final model as well as the use of antianxiety medications (including benzodiazepines) as per the most recent MDS assessment (field O4b).³³ All analyses were performed using SAS® software (version 9.3; SAS Institute Inc., Cary, NC).

RESULTS

The sample consisted of 367 cases and 1468 controls. Among the cases, 311 (84.7%) had only a serious fall, 45 (12.3%) had only a hip fracture, and 11 (3%) had both a serious fall and a hip fracture. Cases were similar to the controls except that cases were more likely to have cognitive impairment (77% vs. 68%) and wandering behavior (12% vs. 7%) (Table 1).

Overall, about 65% of residents were on CNS drugs; 48% on antidepressants, 20% on antiepileptics, 20% on antipsychotics, 5% on benzodiazepine receptor agonist hypnotics, and 25% on opioid receptor agonists. Table 2 shows the CNS medication burden for the five individual classes and overall. Cases compared to controls took higher mean SDDs of antidepressants (1.07 vs 0.76, respectively), antiepileptics (0.24 vs 0.18, respectively), and antipsychotics (0.83 vs 0.47, respectively). On average, the CNS SDD was higher in cases compared with controls, as were the percent taking 3+ CNS SDDs (41% vs. 28%).

Table 3 shows the results from the unadjusted and multivariable analyses. Compared to those not taking any CNS medications, those taking 3+ CNS SDDs had nearly twice the odds (Adjusted Odds Ratio 1.83; 95% CI 1.35–2.48) of serious falls. There was no significant difference in serious fall risk for residents taking >0 to <3 CNS SDDs compared to residents taking no CNS medications (Adjusted Odds Ratio 0.85; 95% CI 0.63–1.15).

Antianxiety medications were more likely to be used by cases than controls (26.2% vs 22.2%, respectively; $p=0.11$). In a sensitivity analysis adjusting for the same final model covariates and also antianxiety medication use, these findings persisted.

DISCUSSION

We found that older nursing home residents with a history of falls and high CNS dosage burden, (i.e., those taking three or more standardized daily doses), had a nearly two-fold increased odds of serious falls. This is consistent with the findings from two previous studies that explored dose-response relationships between CNS medications and falls in older nursing home residents.^{11,12} The first study from the Netherlands focused on fall risk and psychotropic defined daily dosage (DDD) in 248 older nursing home residents with dementia.¹¹ Unlike SDD, DDD is defined by the World Health Organization as the average adult daily dose for the main indication.¹¹ The authors found that those taking a total of 2.5 DDD of antidepressants, antipsychotics, or hypnotics/sedatives had at least a threefold increase in absolute fall risk.¹¹ Their study was limited by the use of a sample restricted to those with dementia, and by failing to include two important CNS classes: antiepileptics or opioids. The second study examined the impact of the combined daily dosage of both anticholinergic and sedative medications (Drug Burden Index [DBI]) on falls in 602 older nursing home residents from Australia.¹² Again, the authors found a nearly two-fold increased odds of falls in those with a higher DBI dosage (> 1).¹² However, they did not report the impact of these two diverse medication classes separately, which is important because there are mixed results regarding the risk of falls with anticholinergic medications.^{34,35} Despite these potential limitations and regardless of the exposure

definition used, it appears that higher CNS medication burden increases the likelihood of falls in older nursing home residents.

The clinical implications of these findings are far-reaching and include pain/discomfort for older nursing home residents and increased health services use and associated costs. For residents with a high CNS burden and taking an unnecessary CNS medication (i.e., no indication, not effective, therapeutic duplication, or too long of a duration), providers should consider discontinuing this CNS medication by cautiously tapering it over a period of time to avoid the small risk of an adverse drug withdrawal event.^{36,37} This is especially true for antiepileptics and benzodiazepine receptor agonists where one might consider tapering over a 21–36 week period.^{38–40} There are times when it will be necessary to add a new CNS medication, and it will not be clinically feasible to discontinue any current CNS medications to reduce overall burden. In these cases, providers should consider reducing the doses of individual CNS medications before prescribing another to mitigate the burden. For example in someone with neuropathic pain in which one is considering the addition of an SNRI, one might be able to reduce the dose of a benzodiazepine receptor agonist as the SNRI is also effective in the treatment of anxiety.⁴¹ Another approach is to consider non-pharmacological alternatives that may be safer than prescribing a new CNS medication.⁴² For example, instead of prescribing a new antipsychotic for behavioral and psychotic symptoms of dementia, non-pharmacological approaches should be considered.⁴³

There are a number of strengths to this study. We used a strong observational design and accurate pharmacy dispensing file data to create an innovative medication exposure measure.¹⁴ The ICD/CPT codes we used to define falls have good face validity as they are included in a NCQA measure and have a good positive predictive validity compared to medical record review.^{20–22} We adjusted for important risk factors for falls in nursing home residents, including indications for CNS medications and comorbidity via the Charlson Comorbidity Index to address potential confounding.^{3,26} However, for non-claims based data, other comorbidity measures such as the Cumulative Illness Rating Scale–Geriatrics may be preferred over the Charlson Comorbidity Index determined by ICD-9 code diagnoses.⁴⁴ To address this in part, we also controlled for number of unique prescription drugs (excluding CNS medications and other drugs that may increase the risk of syncope/falls) to serve as an additional proxy comorbidity measure.⁴⁵ Finally, the findings should generalize to a national target population. There are potential limitations to consider as well. The rate of serious falls may have been affected by the practice patterns of the nursing home facilities. However, we would not expect these to be systematically different across CNS medication exposure groups. We did not have information about the likely small percent of residents with “do not transfer to the emergency room or hospital” orders which could have led to an underestimate of serious falls. We also did not have information about benzodiazepine use as they were not covered by Medicare Part D at the time of the study. This may have led to an underestimate of overall CNS SDD, and it is unknown if any ascertainment bias was differential across cases and controls. We did however adjust for antianxiety medication use in a sensitivity analysis, the bulk of which is likely benzodiazepines, recorded on baseline and quarterly MDS assessments. A recent study showed that there was moderate agreement between antianxiety use as per MDS and pharmacy prescription drug data.³³ Also, we were unable to examine less serious falls

occurring in nursing homes. In addition, we cannot rule out potential residual confounding by unmeasured factors such as diminished safety judgment or confounding by indication (e.g., those with more significant mental health challenges), the latter of which represents a most stubborn bias to remove by analytical means.⁴⁶ Finally, our work may not generalize to short stay, private pay, or Medicare Advantage residents.

In conclusion, greater CNS medication burden, approximately 3+ standardized daily doses, was associated with an increased likelihood of serious falls in nursing home residents with a recent history of falls. Clinicians should be vigilant for opportunities to discontinue or decrease the doses of individual CNS medications and/or consider non-pharmacological alternatives. Such interventions that reduce use of CNS medications in nursing homes could reduce fall rates but further research is needed to confirm this.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics by Group Status

Variables	Controls N=1468		Cases N=367		P value
	n	%	n	%	
Demographics					
Age, Mean (SD) (matching variable; for descriptive purposes only)	84.8	(8.2)	84.8	(8.2)	N/A
Male (matching variable; for descriptive purposes only)	340	23.2	85	23.2	N/A
White, Non-Hispanic	1261	85.9	328	89.4	0.08
Health Status Factors					
Cognitive function					
intact	466	31.7	85	23.2	0.005
mild to moderate impairment	865	58.9	243	66.2	
severe impairment	137	9.3	39	10.6	
Walking aid use	1384	94.3	336	91.6	0.051
Vision Impairment	458	31.2	121	33.0	0.49
Wandering	100	6.8	44	12.0	0.001
Parkinson's disease	72	4.9	26	7.1	0.10
Urinary incontinence	795	54.2	191	52.0	0.47
Charlson Comorbidity Index excluding Dementia, Mean (SD)	5.0	(3.2)	5.1	(3.3)	0.57
Use of other medications that may increase risk of falls/fracture/syncope ^a	155	10.6	43	11.7	0.52
Number of medications at admission excluding those above ^b					
0	271	18.5	56	15.3	
1-3	485	33.0	125	34.1	
4-8	556	37.9	150	40.9	
>=9	156	10.6	36	9.8	
CNS Medication Indications					
Anxiety	970	66.1	233	63.5	0.35
Depression	317	21.6	86	23.4	0.47
Seizure disorder	182	12.4	36	9.8	0.17
Moderate/severe bodily pain	78	5.3	22	6.0	0.60
Dementia medications	562	38.3	122	33.2	0.07
	234	15.9	58	15.8	0.95

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^a Antidepressants other than TCAs, SSRIs, and SNRIs, or peripheral alpha blockers or skeletal muscle relaxants;

^b Excluding antidepressants, antiepileptics, antipsychotics, benzodiazepine receptor agonist hypnotics, opioid receptor agonists, peripheral alpha blockers, and skeletal muscle relaxants.

Abbreviations: CNS = central nervous system; MDS = Minimum Data Set; SD= standard deviation; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Table 2

CNS Medication Standardized Daily Dose by Class and Overall by Group Status, Within 6 Days Prior To the Outcome

CNS Class and Overall SDD Variables	Controls (n=1468) Mean (sd) [IQR]	Cases (N=367) Mean (sd) [IQR]	P value*
Antidepressants (SSRIs or SNRIs or TCAs)	0.76 (1.34) [0.0–1.0]	1.07 (1.55) [0.0–2.0]	<0.001
Antiepileptics	0.18 (0.55) [0–0]	0.24 (0.72) [0–0]	0.05
Antipsychotics	0.47 (2.38) [0–0]	0.83 (2.95) [0–0]	0.02
Benzodiazepine receptor agonist hypnotics	0.08 (0.34) [0–0]	0.06 (0.32) [0–0]	0.37
Opioids receptor agonists	0.97 (2.56) [0–0]	0.88 (1.96) [0–0.65]	0.54
Overall CNS Medication Use	2.45 (4.01) [0–3.2]	3.07 (4.29) [0–4.3]	0.008
CNS SDD Use Categories, n (%)			<0.001
0	520 (35.4)	114 (31.1)	
>0 – <3	537 (36.6)	102 (27.8)	
3+	411 (28.0)	151 (41.1)	

Abbreviations: CNS = central nervous system; IQR= inter quartile range (25th–75th percentile); SD= standard deviation; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; SDD=standardized daily dose; TCA = tricyclic antidepressant

Table 3

Unadjusted and Multivariable Relationship between Standardized Daily Dose of CNS Medications and Serious Falls

Standardized Daily Dose Of CNS Medications	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio ^a (95% CI)
3+	1.75 (1.31–2.33)	1.83 (1.35–2.48)
>0 – <3	0.87 (0.65–1.17)	0.85 (0.63–1.15)
0	Reference	Reference

^aConditional logistic regression adjusted for race/ethnicity, cognitive function, walking aid use, vision impairment, wandering, Parkinson's Disease, urinary incontinence, Charlson Comorbidity Index (excluding dementia), other medication use that may increase risk of falls/fractures/syncope, number of medications (excluding those above), and CNS medication indications (i.e., anxiety, depression, seizure disorder, moderate/severe bodily pain, and dementia medications)

Abbreviations; CI=confidence interval; CNS = central nervous system

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