Published in final edited form as:

Pharmacotherapy. 2019 May ; 39(5): 530–543. doi:10.1002/phar.2244.

The Association Between Central Nervous System-Active Medication Use and Fall-Related Injury in Community-Dwelling Older Adults with Dementia

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Abstract

Objectives: To examine the association between central nervous system (CNS)-active medication use and risk of fall-related injury in community-dwelling older adults following dementia onset. Further, to evaluate increased risk at higher doses or with greater number of CNS-active medication classes.

Methods: Participants included community-dwelling older adults aged ≥ 65 years with a dementia diagnosis participating in the Adult Changes in Thought Study. From automated pharmacy data, a time-varying composite measure of CNS-active medication use was created. Central nervous system-active medication use was classified as: current (use within prior 30 days), recent (prior 31–90 days), past (prior 91–365 days), and non-use (no exposure in prior year). For current users, standardized daily doses (SDDs) were calculated for each CNS-active medication and summed across medications, and the number of CNS-active medication classes used was also measured. The outcome was fall-related injury based on emergency department, inpatient, and outpatient International Classification of Diseases, Ninth Revision (ICD-9) and external cause of injury (E) codes.

Results: Among 793 subjects, there were 303 fall-related injuries over a mean follow-up of 3.7 years (2,907 total person-years). Relative to non-use, fall risk was significantly higher for current use (adjusted hazard ratio [HR] 1.59; 95% confidence interval [CI] 1.19–2.12), but not for past or recent use. Among current users, increased risk was seen across SDD levels; HRs (95% CI): 1.77 (1.19–2.62), 1.79 (1.25–2.56), and 1.35 (0.96–1.92) for <1 SDD, 1 to <2 SDD, and ≥ 2 SDD, respectively (trend test, $p = 0.14$). A trend was seen for increasing risk with greater number of CNS-active medication classes, however, this was not statistically significant (trend test, $p = 0.084$).

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Conflict of interest statement: Laura A. Hart, Zachary A. Marcum, Shelly L. Gray, Rod L. Walker, Paul K. Crane, and Eric B. Larson have no conflicts of interest to disclose.

Conclusions: Current use of CNS-active medications was associated with fall-related injury in community-dwelling older adults followed from time of dementia onset, with increased risk even with use of low doses.

Keywords

CNS-active agents; accidental falls; dementia

Introduction

One in 3 community-dwelling older adults aged 65 years or older falls each year.¹ Among older adults, falls are associated with increased morbidity and mortality, representing the leading cause of fatal and non-fatal injury.¹ In older adults with dementia, the risk of falling is higher, with estimates ranging from 2- to 8-fold greater than those without dementia, and the resulting health outcomes are even more devastating.^{2,3,4,5,6} It is estimated that 5 million individuals in the United States currently have dementia, and with the aging population, this number is expected to climb to 13 million by 2050.^{7,8,9} Thus, identifying modifiable risk factors for falls in older adults with dementia is a public health priority.

While much is known about central nervous system (CNS)-active medication-related risk of falls in older adults without dementia,^{10,11,12,13} important gaps remain in our knowledge of this risk in those with dementia. There is evidence to suggest that older adults with dementia may be more sensitive to the effects of CNS-active medications (e.g., effects on cognition).^{14,15,16} However, few studies to date have examined how CNS-active medications may affect fall risk in older adults with dementia, despite the fact that nearly 80% of community-dwelling older adults with dementia have been prescribed a CNS-active medication.¹⁷ The existing literature on CNS-active medications and falls in older adults with dementia has been largely conducted in institutional settings (e.g., nursing home or hospital), and has found increased risk of falls or fractures associated with various classes of CNS-active medications, including antipsychotics, antidepressants, anxiolytics, and hypnotics.^{18,19,20,21,22} Another major gap in the existing literature is that most studies have focused on individual CNS-active medication classes rather than combined exposures.^{18,21,22,23} This is an important gap given that polypharmacy of CNS-active medications in older adults without dementia has been associated with increased risk of falls,^{24,25,26} and it has been estimated that over half of community-dwelling older adults with dementia have been prescribed a combination of CNS-active medications.¹⁷ Finally, most prior studies have not specified stage of dementia in their eligibility criteria, and thus likely included a heterogeneous sample with regard to stage.^{18,21,22,23}

Bridging these gaps could inform development of future targeted interventions to optimize CNS-active medication use and decrease risk of falls in older adults with dementia at distinct stages, such as the early stages following diagnosis. As such, in the present study, we examined the association between CNS-active medication use and risk of fall-related injury in community-dwelling older adults with a recent diagnosis of dementia. In addition, we examined whether there is increased risk at higher doses or with greater number of CNS-active medication classes.

Methods

Data Source, Study Design, and Sample

This study used data from Adult Changes in Thought (ACT), an ongoing prospective cohort study in which adults aged 65 years and older without dementia have been randomly sampled from Kaiser Permanente Washington (KPW), an integrated health care delivery system in Washington State.²⁷ Participants in the ACT study are interviewed at follow-up study visits every 2 years, at which time a variety of health characteristics are assessed. In addition, cognitive function is assessed using the Cognitive Abilities Screening Instrument (CASI).²⁸ Participants with a CASI score ≥ 85 undergo further in-depth evaluation to determine a diagnosis of dementia using a gold standard research definition.^{29,30} The dementia onset date is defined as the midpoint between the ACT study visit that triggered the dementia evaluation and the prior ACT study visit. Additional ACT study methods have been previously detailed.²⁷ Subjects were included in the present study if they had a diagnosis of dementia as of April 30, 2014, were enrolled in KPW for at least 1 year prior to dementia diagnosis, and had no history of fall-related injury within 1 year prior to dementia diagnosis ($n = 862$). A study flow diagram is depicted in Figure 1.

Outcome Measurement

The outcome of interest was fall-related injury as defined by Tinetti and colleagues,³¹ and modified to include outpatient events. Fall-related injuries were defined based on emergency department, inpatient, and outpatient encounters for injuries that are likely due to falls. Events with a fall-related external cause of injury (E) code and an International Classification of Diseases, Ninth Revision (ICD-9) injury code for nonpathological skull, facial, cervical, clavicle, humeral, forearm, pelvic, hip, fibula, tibia, or ankle fracture; brain injury; or dislocation of the hip, knee, shoulder, or jaw. In the absence of a fall-related E code, events with an ICD-9 injury code were included, provided there was no E code for a motor vehicle accident. Also, inpatient and emergency department visits that were accompanied by a fall-related E code were included regardless of whether they were accompanied by one of the ICD-9 injury codes. A list of ICD-9 codes and E codes included in the definition used for fall-related injury is provided in Appendix Table 1. Frequencies of ICD-9 and E codes for fall-related injury within the entire study sample are summarized in Appendix Table 2.

Exposure Measurement

Central nervous system-active medication use was ascertained from KPW automated pharmacy data, which included outpatient prescription fills at KPW and non-KPW pharmacies. The CNS-active medications included were anticholinergics, antidepressants, antipsychotics, benzodiazepines/sedative hypnotics, opioids, and skeletal muscle relaxants. Central nervous system-active medication exposure was time-varying for individuals during study follow-up and defined in the following mutually exclusive categories: a) current use: medication exposure in the prior 30 days, b) recent use: exposure within the prior 31–90 days but not more recently, c) past use: exposure within the prior 91–365 days but not more recently, and d) non-use: no exposure in the prior 365 days. Medication exposure refers to a

prescription fill providing any medication supply overlapping with the exposure period of interest.

To evaluate a potential dose-response association, total CNS-active medication burden was measured among current users based on standardized daily dose (SDD), which was calculated by dividing the total daily dose of each medication by the minimum effective geriatric dose for that medication (determined via a standard reference)^{32,33} and summing standardized doses of all CNS-active medications for each current user. This approach for calculating SDD has been published in prior studies.^{34,35} In addition to dose, a polypharmacy measure defined as the number of CNS-active medication classes among current users was considered.

Secondary exposures considered the specific medication classes being used, as well as whether use constituted new initiation of a CNS-active medication. For the latter, periods of current use during follow-up were categorized as either new initiation or continued (prevalent) use. New initiation was defined as filling any medication within a CNS-active medication class (e.g., opioids) within the past 30 days with no previous exposure to medications from that class in the 90 days prior to that “new” prescription. All other periods of current use were considered prevalent use. A complete list of CNS-active medications included in the analyses and the corresponding minimum effective doses used to calculate SDD are outlined in Appendix Table 3.

Covariates

Several demographic, health, and functional characteristics were assessed. Demographic covariates were age, ACT study cohort (original, expansion, replacement), sex, race (white or non-white), and education level (education beyond high school or not). Health characteristics gathered from the ACT study visit most proximal to dementia onset were body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), self-rated health (fair/poor vs. good/very good/excellent), poor vision (based on eyesight interview responses or inability to complete CASI test due to poor eyesight), osteoarthritis, coronary artery disease (myocardial infarction, angina, coronary artery bypass graft, or angioplasty), congestive heart failure, and prior stroke. Treatment for hypertension and treatment for diabetes were ascertained via prescription fills from computerized pharmacy data for related medications within 3 years prior to dementia onset. In addition, a performance-based gait speed measure assessed during the ACT study visit most proximal to dementia onset as a measure of frailty (<0.6 meters/second or inability to complete the timed walk) was used. For individuals missing the gait speed measure, self-reported measures of activities of daily living related to walking and reported difficulty walking a half-mile were used for imputation of frail gait speed, when available. To account for potential confounding by indication, several conditions were assessed from clinical diagnosis codes and treated as time-varying (Appendix Table 4). Anxiety, Parkinson’s disease, and urinary incontinence were measured using ICD-9 codes (ever/never), with measurement starting 3 years before dementia onset and continuing through follow-up. Depression was measured using a 10-item Center for Epidemiological Studies Depression (CESD-10) score of 10 or presence of a relevant ICD-9 code, and was also treated as time-varying (ever/never) with a 3-year look-

back period. Behavioral disturbances of dementia and insomnia or sleep problems were also measured using ICD-9 codes and treated as time-varying (active/inactive), being updated over time with a 12-month look-back period to capture their potentially episodic nature.

Statistical Analyses

For all analyses, participants were followed until the earliest of fall-related injury or a censoring event (ACT or health plan disenrollment, death, or April 30, 2014). For the primary analysis, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of fall-related injury associated with CNS-active medication use (current, recent, or past) compared with no use as the reference group. These models used time since dementia onset as the time axis and were adjusted for the following covariates: age (modeled using a natural cubic spline),³⁶ ACT cohort, sex, BMI, self-rated health, slow gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, coronary artery disease, poor vision, congestive heart failure, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia. Furthermore, HRs were estimated for risk of fall-related injury associated with level of SDD among current users (<1 SDD, 1 to <2 SDD, or ≥2 SDD) compared with no use as the reference group. In addition, HRs for risk of fall-related injury associated with number of CNS-active medication classes among current users (1 class, 2 classes, or ≥3 classes) compared with no use as the reference group were estimated. A trend test was used to evaluate a potential dose-response association across SDD levels, as well as to evaluate risk across numbers of medication classes.

As a secondary analysis, HRs were estimated for risk of fall-related injury associated with current use of the five most commonly used classes of CNS-active medications among the study subjects; these classes were antidepressants, antipsychotics, benzodiazepines/sedative hypnotics, opioids, and urinary antispasmodics (a subclass within anticholinergics). For an additional secondary analysis, HRs were estimated for risk of fall-related injury associated with new initiation of a CNS-active medication. In this analysis, any new initiation of a CNS-active medication and prevalent use of a CNS-active medication (without new initiation) were compared with no use as the reference group. Furthermore, for this new-initiation analysis only, we restricted the study sample to participants with no evidence of a prescription fill for a CNS-active medication within the year prior to dementia onset so as to start with a sample of non-users. All analyses used a complete case analysis, excluding subjects with missing covariate data.

Examination of Schoenfeld residuals showed some evidence of non-proportional hazards for the comparison of current use to non-use of CNS-active medications. Thus, a post-hoc analysis was conducted in which the primary analysis was repeated, but truncated follow-up at 1 year, 3 years, and 5 years, respectively, so as to investigate the impact of follow-up time on the estimated (time-averaged) HR. Another post-hoc analysis focused on using a lower minimum effective dose for opioids (morphine 10 mg vs. 30 mg), as was used in a study published after this study was implemented.³⁷

Results

By April 30, 2014, 1,032 ACT subjects had a diagnosis of dementia. From this cohort, 63 subjects were excluded due to not having at least 1 year of enrollment in KPW prior to dementia diagnosis. In addition, 107 subjects were excluded due to evidence of fall-related injury within 1 year prior to dementia diagnosis. This resulted in a sample of 862 subjects. The median age of the sample at baseline (dementia onset) was 85 years, 62% of individuals were female, and 91% were white. Additional baseline characteristics and covariate information for the sample, subdivided by category of CNS-active medication use at baseline, are detailed in Table 1. Of the 862 subjects, 335 (39%) were current users of any CNS-active medication, 57 (7%) were recent users, 106 (12%) were past users, and 364 (42%) were non-users.

Among the 793 subjects with complete covariate data used for primary analyses, there were 303 fall-related injuries over a mean follow-up of 3.7 years (2,907 total person-years). Compared to non-users of CNS-active medications, current users had an increased risk of fall-related injury (adjusted HR 1.59, 95% CI 1.19–2.12) (Table 2). However, increased risk of fall-related injury was not observed for recent users (adjusted HR 0.94, 95% CI 0.52–1.69) or past users (adjusted HR 0.84, 95% CI 0.55–1.29), compared to non-users. When we examined the relationship between dose (as measured by SDD) and risk of fall-related injury among current users, no dose-response association was detected (test for trend, $p = 0.14$). When the risk of fall-related injury associated with increasing number of CNS-active medication classes was evaluated, a trend was seen for increasing risk with greater number of medication classes, but this was not statistically significant (test for trend, $p = 0.084$).

Table 3 and Table 4 outline the results of the secondary analyses. Among current users of specific classes of CNS-active medications, only current use of antidepressants and opioids had a significant association with risk of fall-related injury, with adjusted HRs of 1.41 (95% CI 1.06–1.87) and 1.69 (95% CI 1.22–2.33), respectively (Table 3). The point estimate for benzodiazepines/sedative hypnotics was in the direction of increased risk, but did not achieve statistical significance (adjusted HR 1.31, 95% CI 0.85–2.02). The adjusted HR for risk of fall-related injury associated with any new initiation of a CNS-active medication compared with no use was 1.86 (95% CI 0.85–4.09) (Table 4).

On post-hoc analysis, the contrast in fall-related injury hazards between current use and non-use of CNS-active medications appeared greatest soon after dementia onset, with a decline in the estimated HR when including greater follow-up time following dementia onset. More specifically, the adjusted HRs (95% CIs) for the 1 year, 3 year, and 5 year follow-up analyses after dementia diagnosis were 2.49 (1.45–4.28), 1.75 (1.22–2.53), and 1.66 (1.21–2.27), respectively. There was also no dose-response association detected in the post-hoc analysis using the lower dose of morphine for calculating opioid SDDs (test for trend, $p = 0.439$).

Discussion

In this sample of community-dwelling older adults followed from time of dementia onset, current use of CNS-active medications was associated with a 59% increased hazard of fall-related injury compared to non-use over a mean follow-up of 3.7 years. However, an increased risk was not observed for recent use or past use compared to non-use. In addition, the risk of fall-related injury observed with current CNS-active medication use was elevated across dose levels (SDD) and across groups defined by numbers of concurrent CNS-active medication classes being used, even for participants in the lowest use categories. However, risk may vary across medication classes.

To the best of our knowledge, this is the first study in older adults with dementia that evaluated an overall composite measure of CNS-active medication use, which included several medication classes and the dose of each medication. Comparing this study to prior literature on CNS-active medication-related falls in older adults with dementia is challenging because of differences in study design and CNS-active medication exposure definition, as well as the inclusion of patients at varying stages of dementia. It was unexpected that a dose-response relationship was not observed in the present study, as prior literature has found that use of higher doses and use of multiple CNS-active medications increase risk of falls in older adults without dementia.^{24,25} It is important to note that an elevated risk of fall-related injury was found even at low SDDs. Further, CNS-active medication polypharmacy showed a trend of increasing hazard of fall-related injury with greater number of concurrent CNS-active medication classes, though this did not quite achieve statistical significance. The evaluation of potential risks associated with use of multiple CNS-active medications is important considering most older adults with dementia prescribed a CNS-active medication are using more than 1 CNS-active medication.¹⁷ Thus, this analysis of multiple CNS-active medications aligns with how these medications are often used in clinical practice.

One strength of this study is that it focused on a well-defined sample of older adults with dementia who were examined starting from the time of dementia onset. Two prior studies focused on the same sample of nursing home residents with advanced stage dementia,^{19,20} however, most studies did not specify stage of dementia in their eligibility criteria.^{18,21,22,23} This is an important consideration, given that there may be differences in sensitivity to CNS-active medications or a different pattern of use as dementia progresses.

Moreover, most prior studies evaluating risk of falls or fractures in older adults with dementia have focused on single medication classes, finding increased risk with antidepressants,^{19,20} anticholinergics,²³ antipsychotics,^{19,21} benzodiazepines,¹⁹ sedatives/hypnotics,^{18,19} and opioids.²³ In the current study, antidepressants and opioids independently demonstrated a significant association with increased risk of fall-related injury. The point estimate for benzodiazepines/sedative hypnotics also suggested an increased risk (HR of 1.31), though this was not statistically significant. The significant association noted with opioids is consistent with findings from the only other study conducted in community-dwelling older adults with dementia (specifically Alzheimer's disease), where opioids and anticholinergics were found to be associated with fall-related injury.²³ The significant association for antidepressants in the present study is consistent

with results of studies conducted in older adults with dementia in institutionalized settings.^{19,20} The other medication classes evaluated in this analysis (antipsychotics and urinary antispasmodics) did not have a significant association. The lack of findings of significant associations for some of the medication classes should be interpreted cautiously given the relatively low prevalence of use in the sample.

Initiation of a new CNS-active medication is a time of considerable risk for falling for older adults.^{38,39} The results of the secondary analysis provided some support that this is a problem for those with dementia. This study found an increased risk (HR of 1.86) for fall-related injury associated with new initiation of a CNS-active medication compared with no use. While this point estimate was in the direction of an increased risk, it was not statistically significant. It is plausible that this secondary analysis lacked power to detect this association given the small sample size and low event rate. Ultimately, this association will need to be evaluated in a larger sample.

The post-hoc analysis evaluating the impact of follow-up time on the estimated HR for risk of fall-related injury suggested the risk associated with current use of CNS-active medications may be greatest soon after dementia onset. A possible reason for this finding is that the sample of individuals who did not experience fall-related injury initially and who survived to the later time points of study follow-up may not be representative of the CNS-active medication users/non-users around the time of dementia onset. Other explanations for this finding include more cautious prescribing of CNS-active medications as dementia progresses or differing patterns of CNS-active medications used as dementia progresses. These findings should be considered hypothesis-generating, and additional evaluation is needed to better understand how CNS-active medication-related fall risk may change over time following dementia onset.

The present study has strengths worth mentioning. One strength is that individuals with dementia were identified using a research-quality dementia diagnosis, rather than claims-based diagnosis codes, resulting in a study cohort for which dementia was well characterized and valid. Additionally, it was possible to measure total CNS-active medication burden, in addition to number of CNS-active medication classes, and evaluate how these factors may influence risk of fall-related injury. Another strength was the ability to use ACT study visit data in addition to administrative claims data, allowing for adjustment of several important covariates to minimize confounding (e.g., gait speed) that we would not have been able to adjust for using administrative claims data alone.

There are also limitations to note. One limitation is that the study relied on automated pharmacy data to ascertain exposure of CNS-active medication use, making misclassification of exposure a possibility due to potential unmeasured use of over-the-counter medications. However, this issue would be limited to the anticholinergic medications (e.g., antihistamines), as all other CNS-active medications included in this study were only available with a prescription. In addition, there is the possibility that an individual received a prescription for a CNS-active medication but never actually used the medication, which could also result in misclassification of exposure. Also, the study could not differentiate between as needed and regularly scheduled medications. Like any pharmacoepidemiologic

study, there is also the possibility of unmeasured or residual confounding. Moreover, it was not possible to assess the association between severity of dementia and fall-related injury given the design of the ACT study (i.e., participants are no longer administered structured interviews after receiving a dementia diagnosis).

In conclusion, this study found that current use of CNS-active medications was associated with fall-related injury in community-dwelling older adults followed from time of dementia onset, with increased risk even with use of low doses. These results highlight the need for judicious use and close monitoring of CNS-active medications in this high-risk patient population. Pharmacists and other clinicians should make an active effort to address medication use as part of a comprehensive effort to prevent falls. Resources on comprehensive fall risk assessment and strategies to reduce risk are freely available from the Centers for Disease Control and Prevention as part of the STEADI (Stopping Elderly Accidents, Deaths & Injuries) Toolkit.⁴⁰

Acknowledgements:

This analysis was supported by grant funding from the American College of Clinical Pharmacy Research Institute (Futures Grant Junior Investigator Award), and the National Institute on Aging (U01AG006781).

Appendices

Appendix Table 1.

ICD-9 and E codes used for fall-related injury

ICD-9 or E Code	Definition
Fracture	
800	Fracture of vault of skull
801	Fracture of base of skull
802	Fracture of face bones
803	Other and unqualified skull fractures
804	Multiple fractures involving skull or face with other bones
805	Fracture of vertebral column without mention of spinal cord injury
806	Fracture of vertebral column with spinal cord injury
807.0–807.2	Fracture of rib(s), sternum, larynx, and trachea
808.0–808.9	Fracture of pelvis
810	Fracture of clavicle
811	Fracture of scapula
812	Fracture of humerus
813	Fracture of radius and ulna
814	Fracture of carpal bone(s)
815	Fracture of metacarpal bone(s)
816	Fracture of one or more phalanges of hand
817	Multiple fractures of hand bones
818.0–818.1	Ill-defined fractures of upper limb

ICD-9 or E Code	Definition
819.0–819.1	Multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
820	Fracture of neck of femur
821	Fracture of other and unspecified parts of femur
822	Fracture of patella
823	Fracture of tibia and fibula
824	Fracture of ankle
825	Fracture of one or more tarsal and metatarsal bones
826	Fracture of one or more phalanges of foot
827	Other multiple and ill-defined fractures of lower limb
828	Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum
829	Fracture of unspecified bones
Intracranial Injury	
850	Concussion
851	Cerebral laceration and contusion
852	Subarachnoid subdural and extradural hemorrhage following injury
853	Other and unspecified intracranial hemorrhage following injury
854	Intracranial injury of other and unspecified nature
Dislocation	
830	Dislocation of jaw
831	Dislocation of shoulder
832	Dislocation of elbow
833	Dislocation of wrist
834	Dislocation of finger
835	Dislocation of hip
836	Dislocation of knee
837	Dislocation of ankle
838	Dislocation of foot
839	Other multiple and ill-defined dislocations
Contusion	
920	Contusion of face, scalp, and neck except eye(s)
921	Contusion of eye and adnexa
922	Contusion of trunk
923	Contusion of upper limb
924	Contusion of lower limb and of other and unspecified sites
Accidental Fall	
E880	Accidental fall on or from stairs or steps
E881	Accidental fall on or from ladders or scaffolding
E882	Accidental fall from or out of building or other structure
E883	Accidental fall into hole or other opening in surface

ICD-9 or E Code	Definition
E884	Other accidental falls from one level to another
E885	Accidental fall on same level from slipping tripping or stumbling
E886	Fall on same level from collision, pushing, or shoving, by or with other person
E887	Fracture, cause unspecified
E888	Other and unspecified fall
V15.88	History of falls

Abbreviations: E code = external cause of injury code; ICD-9 = International Classification of Diseases, Ninth Revision

Appendix Table 2.

Frequencies of ICD-9 and E codes for fall-related injury within entire study sample

	Fall-related injuries		Inpatient/ED		Outpatient	
	N	%	N	%	N	%
Total	328		215		113	
Lower limb fracture	122	37.2	77	35.8	45	39.8
Upper limb fracture	65	19.8	34	15.8	31	27.4
Ribs or sternum fracture	37	11.3	12	5.6	25	22.1
Vertebral column fracture	25	7.6	22	10.2	3	2.7
Pelvic fracture	18	5.5	14	6.5	4	3.5
Skull or facial fracture	13	4.0	10	4.7	3	2.7
Intracranial injury (excluding skull fracture)	11	3.4	11	5.1	0	0.0
Dislocation	11	3.4	6	2.8	5	4.4
	N	%	N	%	N	%
Total	328		215		113	
Only injury (ICD-9) codes, no fall-related E codes [†]	177	54.0	82	38.1	95	84.1
Both injury and fall-related E codes	98	29.9	80	37.2	18	15.9
Only fall-related E codes, no injury codes	53	16.2	53	24.7	0	0.0

Abbreviations: E code = external cause of injury code; ED = emergency department; ICD-9 = International Classification of Diseases, Ninth Revision

[†]Injury codes without fall-related E codes were counted as fall-related injuries, provided there was no E code for a motor vehicle accident (E810.0–819.9)

Appendix Table 3.

CNS-active medications included in analysis and corresponding geriatric dose used to calculate standardized daily dose.

Drug Class	Individual Medications	Minimum Effective Geriatric Daily Dose
Benzodiazepines, Anxiolytics, and Sedative/Hypnotics		
Benzodiazepines	Alprazolam	0.25 mg
	Chlordiazepoxide	10 mg
	Clonazepam	0.5 mg
	Clorazepate	7.5 mg

Drug Class	Individual Medications	Minimum Effective Geriatric Daily Dose
	Diazepam	1 mg
	Eszopiclone	1 mg
	Flurazepam	15 mg
	Lorazepam	0.5 mg
	Oxazepam	20 mg
	Temazepam	7.5 mg
	Triazolam	0.0625 mg
Nonbenzodiazepine Benzodiazepine-Receptor Agonists	Zaleplon	5 mg
	Zolpidem	5 mg
Other	Buspirone	15 mg
	Chloral hydrate	250 mg
Opioids		
	Codeine	200 mg (0.15) [†]
	Dihydrocodeine	120 mg (0.25)
	Fentanyl transdermal	12.5 mg (2.4)
	Hydrocodone	30 mg (1.00)
	Hydromorphone	7.5 mg (4.00)
	Levorphanol	2.7 mg (11.00)
	Meperidine	300 mg (0.10)
	Methadone	10 mg (3.00)
	Morphine	30 mg [‡]
	Opium tinctures/suppositories	300 mg (0.10)
	Oxycodone	20 mg (1.5)
	Pentazocine	81.1 mg (0.37)
	Propoxyphene	130.4 mg (0.23)
	Tramadol	300 mg (0.10)
Antipsychotics		
Anticholinergic	Chlorpromazine	10 mg
	Clozapine	12.5 mg
	Mesoridazine	100 mg
	Olanzapine	5 mg
	Pimozide	1 mg
	Thioridazine	10 mg
	Trifluoperazine	0.5 mg
Non-Anticholinergic	Aripiprazole oral	10 mg
	Fluphenazine	1 mg
	Haloperidol oral	0.5 mg
	Lurasidone	40 mg
	Perphenazine (all combinations)	12 mg

Drug Class	Individual Medications	Minimum Effective Geriatric Daily Dose
	Quetiapine	50 mg
	Risperidone oral	1 mg
	Thiothixene	6 mg
	Ziprasidone	40 mg
Antidepressants		
Anticholinergic: Secondary Amine TCA	Amoxapine	50 mg
	Desipramine	25 mg
	Maprotiline	25 mg
	Nortriptyline	30 mg
	Protriptyline	5 mg
Anticholinergic: Tertiary Amine TCA	Amitriptyline	10 mg
	Clomipramine	25 mg
	Doxepin	10 mg
	Imipramine	25 mg
Anticholinergic: Other (SSRI)	Paroxetine	10 mg
Non-Anticholinergic: SSRIs	Citalopram	20 mg
	Escitalopram	10 mg
	Fluoxetine	20 mg
	Fluvoxamine	50 mg
	Sertraline	25 mg
Non-Anticholinergic: SNRIs	Duloxetine	20 mg
	Venlafaxine	50 mg
Non-Anticholinergic: MAOIs	Isocarboxazid	20 mg
	Phenelzine	7.5 mg
	Tranylcypromine	30 mg
Non-Anticholinergic: Other	Bupropion	150 mg
	Mirtazapine	15 mg
	Nefazodone	100 mg
	Trazodone	25 mg
Skeletal Muscle Relaxants		
Anticholinergic	Cyclobenzaprine	5 mg
	Orphenadrine	200 mg
Non-Anticholinergic	Baclofen	10 mg
	Carisoprodol	750 mg
	Dantrolene	25
	Metaxalone	2,400 mg
	Methocarbamol	600 mg
	Tizanidine hydrochloride	12 mg
Anticholinergics		

Drug Class	Individual Medications	Minimum Effective Geriatric Daily Dose
Antihistamines	Azatadine	2 mg
	Cyproheptadine	4 mg
	Hydroxyzine	75 mg
	Trimeprazine	10 mg
Antivertigo/Antiemetic	Prochlorperazine	15 mg
	Promethazine	50 mg
	Scopolamine patch	0.33 mg
Anti-Parkinson's	Benzotropine	0.5 mg
	Procyclidine	2.5 mg
	Trihexyphenidyl	6 mg
Genitourinary Antispasmodic	Darifenacin	7.5 mg
	Flavoxate	300 mg
	Oxybutynin oral	5 mg
	Solifenacin	5 mg
	Tolterodine	2 mg
	Trospium	20 mg
Gastrointestinal Anticholinergic/ Antispasmodic	Atropine	0.0582 mg
	Belladonna suppository	1 suppository
	Levorotatory alkaloids of belladonna	1 tablet
	Clidinium/chlordiazepoxide	7.5 mg
	Dicyclomine	40 mg
	Glycopyrrolate	0.6 mg
	Homatropine	6 mg
	Hyoscyamine	0.75 mg
	Isopropamide	10 mg
	Methantheline	100 mg
	Methscopolamine	10 mg
	Propantheline bromide	22.5 mg
Other		
Belladonna Extract	Alkaloids of belladonna leaf [§]	
Antiarrhythmic IA	Disopyramide	400 mg

Abbreviations: CNS = central nervous system; MAOI = monamine oxidase inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressants

[†]For opioids, number in parentheses after dose refers to morphine equivalents

[‡]In post-hoc analysis, 10 mg was used instead of 30 mg for minimum effective geriatric dose and calculation of morphine equivalents

[§]Belladonna extract (16 mg) = 0.2 of alkaloids of belladonna leaf; each 0.2 mg of belladonna leaf = 0.0582 mg atropine, 0.0195 mg scopolamine, 0.3111 mg hyoscyamine

Appendix Table 4.

ICD-9 codes used for covariates

ICD-9 Code	Definition
Depression	
296.2	Major depressive disorder, single episode
296.3	Major depressive disorder, recurrent episode
298.0	Depressive type psychosis
311	Depressive disorder, not elsewhere classified
300.4	Dysthymic disorder
301.12	Chronic depressive personality disorder
309.1	Prolonged depressive reaction
Anxiety	
300.0	Anxiety states
300.2	Phobic disorders
309.2	Adjustment disorder
Parkinson's Disease	
332.0	Primary Parkinsonism
Insomnia	
780.5	Sleep disturbances
327.0	Organic sleep disorders of initiating and maintaining sleep
Urinary Incontinence	
788.3	Urinary incontinence, unspecified
Behavioral Disturbances of Dementia	
293.0	Agitation

Abbreviations: ICD-9 = International Classification of Diseases, Ninth Revision

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Figure 1. Eligibility criteria and sample size

Abbreviations: ACT = Adult Changes in Thought; BMI = body mass index; KPW = Kaiser Permanente Washington

Table 1.

Characteristics of participants at time of dementia onset, by CNS-active medication exposure

	<u>All Participants</u>		<u>CNS-Active Medication Exposure Classification</u>							
	N = 862		Non-Use		Past Use		Recent Use		Current Use	
	N [†]	%	N	%	N	%	N	%	N	%
Age, median (25 th , 75 th)	85	(81, 89)	84	(80, 88)	84	(80, 88)	86	(83, 89)	85	(81, 89)
BMI, median (25 th , 75 th)	26	(23, 29)	26	(23, 29)	27	(23, 30)	26	(23, 30)	26	(24, 30)
Sex										
Female	530	61.5	216	59.3	57	53.8	42	73.7	215	64.2
Race										
White	781	90.6	329	90.4	96	90.6	54	94.7	302	90.1
ACT cohort										
Original	621	72.0	256	70.3	81	76.4	39	68.4	245	73.1
Expansion	161	18.7	73	20.1	17	16.0	15	26.3	56	16.7
Replacement	80	9.3	35	9.6	8	7.5	3	5.3	34	10.1
Some education beyond high school	492	57.1	208	57.1	62	58.5	32	56.1	190	56.7
Fair or poor self-rated health	189	22.2	53	14.7	28	26.4	10	17.5	98	30.0
Frail according to gait speed	237	29.4	89	25.6	36	36.4	16	29.6	96	31.4
Treatment for hypertension	601	69.7	227	62.4	72	67.9	44	77.2	258	77.0
Treatment for diabetes	91	10.6	35	9.6	10	9.4	5	8.8	41	12.2
Osteoarthritis	577	66.9	229	62.9	64	60.4	40	70.2	244	72.8
Coronary artery disease	244	28.3	81	22.3	34	32.1	18	31.6	111	33.1
Poor vision	361	41.9	146	40.1	48	45.3	22	38.6	145	43.3
Congestive heart failure	88	10.2	24	6.6	14	13.2	4	7.0	46	13.7
Stroke	76	8.8	28	7.7	13	12.3	5	8.8	30	9.0
Anxiety	105	12.2	13	3.6	16	15.1	11	19.3	65	19.4
Depression (CESD score or ICD-9 code)	289	33.5	49	13.5	38	35.8	19	33.3	183	54.6
Urinary incontinence	149	17.3	35	9.6	25	23.6	13	22.8	76	22.7
Parkinson's disease	19	2.2	5	1.4	5	4.7	0	0.0	9	2.7
Insomnia or sleep problems	60	7.0	5	1.4	5	4.7	5	8.8	45	13.4
Behavioral disturbances of dementia	11	1.3	2	0.5	2	1.9	0	0.0	7	2.1

Abbreviations: ACT = Adult Changes in Thought; BMI = body mass index; CESD = Center for Epidemiological Studies Depression; CNS = central nervous system; ICD-9 = International Classification of Diseases, Ninth Revision

[†]Data are presented as N and % unless otherwise noted. Column percentages based on non-missing data. Missing data for each variable: BMI (n = 9), self-rated health (n = 11), and gait speed (n = 55).

Table 2.

Association between CNS-active medication use and fall-related injury in older adults with dementia

CNS-Active Medication Use Group	Person-Years	Fall-Related Injury Rate [†]	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [‡]
None	1,160	8.3	1.00 (Reference)	1.00 (Reference)
Past	392	7.4	0.88 (0.58, 1.33)	0.84 (0.55, 1.29)
Recent	156	8.3	0.98 (0.55, 1.76)	0.94 (0.52, 1.69)
Current	1,199	13.8	1.68 (1.30, 2.16)	1.59 (1.19, 2.12)
Dose Category (SDD)[§]				
<1 SDD	230	16.5	1.99 (1.36, 2.89)	1.77 (1.19, 2.62) [*]
1 to <2 SDD	362	16.0	1.95 (1.40, 2.70)	1.79 (1.25, 2.56)
2 SDD	607	11.4	1.39 (1.02, 1.90)	1.35 (0.96, 1.92)
Number of CNS-Active Medication Classes[§]				
1 class	818	12.8	1.55 (1.17, 2.04)	1.48 (1.09, 2.02) ^{**}
2 classes	294	15.0	1.86 (1.30, 2.66)	1.79 (1.20, 2.67)
3 classes	87	18.3	2.31 (1.36, 3.94)	2.29 (1.30, 4.05)

Abbreviations: ACT = Adult Changes in Thought; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CNS = central nervous system; HR = hazard ratio; SDD = standardized daily dose

[†]Per 100 person-years

[‡]Adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, CAD, poor vision, CHF, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia.

[§]Reference group is no CNS-active medication use

^{*}The p-value for the trend test was 0.140

^{**}The p-value for the trend test was 0.084

Table 3.

Association between use of individual classes of CNS-active medications and fall-related injury in older adults with dementia

CNS-Active Medication Class	Person-Years	Fall-Related Injury Rate [†]	Unadjusted HR [‡] (95% CI)	Adjusted HR (95% CI) ^{‡§}
Antidepressants	811	13.7	1.42 (1.11, 1.80)	1.41 (1.06, 1.87)
Antipsychotics	167	12.0	1.06 (0.66, 1.71)	1.06 (0.65, 1.71)
Benzodiazepines and sedative hypnotics	170	15.8	1.23 (0.81, 1.86)	1.31 (0.85, 2.02)
Opioids	262	19.1	1.82 (1.33, 2.50)	1.69 (1.22, 2.33)
Anticholinergics				
Urinary antispasmodics	194	11.4	0.96 (0.62, 1.48)	0.94 (0.59, 1.49)

Abbreviations: ACT = Adult Changes in Thought; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CNS = central nervous system; HR = hazard ratio

[†] Per 100 person-years

[‡] Current use versus no use as reference group

[§] Adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, CAD, poor vision, CHF, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia. Also adjusted for concurrent CNS-active medication use.

Table 4.

Association between new initiation of CNS-active medication and fall-related injury in older adults with dementia

CNS-Active Medication Use Group	Person-Years	Fall-Related Injury Rate[†]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)^{††}
None	1,079	8.0	1.00 (Reference)	1.00 (Reference)
Prevalent current use	248	9.7	1.23 (0.77, 1.97)	1.30 (0.76, 2.21)
New initiation	50	14.0	1.76 (0.81, 3.81)	1.86 (0.85, 4.09)

Abbreviations: ACT = Adult Changes in Thought; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CNS = central nervous system; HR = hazard ratio

^{††} Adjusted for the following covariates: age, ACT cohort, sex, BMI, self-rated health, gait speed (or self-reported measure), treatment for hypertension, treatment for diabetes, osteoarthritis, CAD, poor vision, CHF, prior stroke, anxiety, depression, urinary incontinence, Parkinson's disease, insomnia or sleep problems, and behavioral disturbances of dementia.

[†] Per 100 person-years.