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Central nervous system medication use and incident mobility limitation in community elders: the health, aging, and body composition study,,†,‡,§

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SUMMARY

Purpose—To evaluate whether CNS medication use in older adults was associated with a higher risk of future incident mobility limitation.

Methods—This 5-year longitudinal cohort study included 3055 participants from the health, aging and body composition (Health ABC) study who were well-functioning at baseline. CNS medication use (benzodiazepine and opioid receptor agonists, antipsychotics, and antidepressants) was determined yearly (except year 4) during in-home or in-clinic interviews. Summated standardized daily doses (low, medium, and high) and duration of CNS drug use were computed. Incident mobility limitation was operationalized as two consecutive self-reports of having any difficulty walking 1/4 mile or climbing 10 steps without resting every 6 months after baseline. Multivariable Cox

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proportional hazard analyses were conducted adjusting for demographics, health behaviors, health status, and common indications for CNS medications.

Results—Each year at least 13.9% of participants used a CNS medication. By year 6, overall 49% had developed incident mobility limitation. In multivariable models, CNS medication users compared to never users showed a higher risk for incident mobility limitation (adjusted hazard ratio (Adj. HR) 1.28; 95% confidence interval (CI) 1.12–1.47). Similar findings of increased risk were seen in analyses examining dose– and duration–response relationships.

Conclusions—CNS medication use is independently associated with an increased risk of future incident mobility limitation in community dwelling elderly. Further studies are needed to determine the impact of reducing CNS medication exposure on mobility problems.

Keywords

aged; mobility; central nervous system drugs

INTRODUCTION

Maintaining functional status is a cornerstone of care for elders. Independent mobility is a critical element of independent function.[1] Mobility limitation causes problems with independent living such as shopping or traveling and can contribute to social isolation.[1] Incident mobility limitation is common among community dwelling older adults; within 5 years, 44% of participants in the health, aging and body composition (Health ABC) study reported new onset mobility limitations, defined as difficulty walking 1/4 mile or climbing 10 steps.[2] The development of incident mobility limitation has prognostic significance; it is associated with increased future health services use and mortality.[3,4]

Although much is known about factors that contribute to incident mobility limitations, few studies have examined the potential contribution of adverse medication effects. Benzodiazepines have been shown to increase the risk of self-reported mobility problems and decline in measured physical performance.[5-7] Antipsychotic drug use has also been shown to predict performance decline.[7] Studies of individual drug classes provide some insights, but since older adults take multiple drugs simultaneously, their combined effect on risk is clinically relevant and potentially greater than use of single classes.[8]

The objective of this study is to evaluate whether the time-varying use of one or more CNS medications from multiple classes increases risk of incident mobility limitations among community dwelling elderly. We defined incident mobility limitation as two consecutive reports of difficulty walking 1/4 mile or climbing 10 steps. We also examine the additional effects of cumulative dose or duration of exposure.

METHODS

Study design, sample and source of data

Longitudinal data were collected from 3075 black and white men and women aged 70–79 with no reported difficulty walking for 1/4 mile, climbing 10 steps, or performing basic activities of daily living, who lived in specified zip code areas surrounding Pittsburgh and Memphis, USA. Community dwelling individuals meeting the above criteria were enrolled between 1997 and 1998 into the Health ABC study and have been followed semi-annually.[9] This study uses the first 6 years of data collection, encompassing the baseline examination and 5 years of follow-up. Twenty participants were excluded from this analysis due to insufficient medication use information at baseline, leaving a sample of 3055 participants included in the analysis. This study was approved by the University of Pittsburgh and University of Tennessee Memphis

Institutional Review Boards and informed consent was obtained from each participant prior to data collection.

Data collection and management

The information collected over a 6-year period included a battery of detailed physiologic and performance measurements and questionnaire material regarding sociodemographic characteristics, multiple aspects of health status, and medication use. For medications, at baseline (year 1) and annually through year 5 (except year 4), participants were asked to bring to clinic all medications they had taken in the previous 2 weeks. Well trained examiners transcribed from the medication containers information on medication name, strength, dosage form, whether the medication was taken as needed, the number of times the respondent reported taking the product the previous day, week, or month, and when they started the medication. The medication data collected was coded using the Iowa Drug Information System (IDIS) codes and then entered into a computerized database.[10]

CNS medication use exposure

We derived the primary independent variable, CNS medication use, from the computerized files of participants' coded prescription medications. Consistent with previous work, we defined CNS medications as those belonging to the following classes: opioid receptor agonist analgesics (IDIS class code 28080800), antidepressants (IDIS class codes 28160500–28160700), antipsychotics (IDIS class codes 28160800–28161000) and benzodiazepine receptor agonists (IDIS class codes 28240200).[11]

We decided *a priori* to test the relationship between time varying exposure to any CNS medication, dosage, duration, and incident mobility limitation. For current users of each regularly scheduled individual CNS medication at baseline (year 1) and years 2, 3, 5, we calculated the average daily dose by multiplying the number of dosage forms taken the previous day by medication strength. The average daily dose was then converted to a standardized daily dose by dividing it by the minimum effective dose per day recommended for elders according to a well respected geriatric pharmacotherapy reference.[12] Thus, a person taking 1.0 standardized CNS medication unit will have taken the minimum recommended effective daily dose for elders for one agent.[13] Using benzodiazepine receptor agonists as an example, the minimum effective geriatric dose per day for individual agents is as follows: alprazolam (0.75 mg), clonazepam (0.5 mg), clorazepate (15 mg), chlordiazepoxide (15 mg), diazepam (4 mg), estazolam (1 mg), flurazepam (15 mg), lorazepam (2 mg), oxazepam (30 mg), temazepam (15 mg), triazolam (0.125 mg), zaleplon (5 mg), and zolpidem (5 mg). This procedure was performed for each CNS medication taken. The individual CNS agent standardized daily doses were then summated to create an overall CNS standardized daily dosage. CNS standardized daily dosage was operationally defined based on the data distribution and clinical relevance into three categories: low dose (<1.0 standardized daily dose), medium dose (>1.0–3.0 standardized daily dose) and high dose (>3.0 standardized daily dose). A list of all specific medications included and their minimum effective daily dose is available upon request from the second author. We also operationally defined, based on the data distribution, time-varying independent categorical variables for the duration of CNS medications use. At baseline, duration of use was operationally defined as either "long-term" (continuous use for previous 2 years) or "short-term" (use only at the baseline in-person medication review). At follow-up years 2, 3, and 5, duration of use among current users was operationally defined as either long-term (use of any CNS medications at most recent and previous in-person medication reviews) or short-term (use at most recent in-person medication review only). No CNS medication use was the reference group for all analyses.

Outcome variables

Based on annual clinic visits and semi-annual phone or proxy contacts, incident mobility limitation was operationally defined as two consecutive self-reports of having any difficulty walking 1/4 mile or climbing 10 steps without resting.[2] A single report of difficulty followed by death of prior to the next scheduled contact was also classified as an event if an adjudicated decedent proxy interview report indicated that the difficulty had been present for more than 6 months. The time to an incident mobility limitation was defined as the time from baseline to the first of the two successive reports of difficulty with the same activity. Followup was through 78 months after baseline with a mean (SD) of 4.2 (2.4) years.

Covariates

Data collected are considered highly accurate and complete and allow assessment of common confounders[9,10] We adjusted for potential confounding variables that may influence the relationship between CNS medication use and incident mobility limitation.[2-7] Sociodemographic factors were represented by dichotomous variables for gender, site, living alone, and race. Race was self-reported as being either black or white. A continuous variable was created for age and a categorical variable for education (post secondary education, high school graduate, and less than high school graduate). Health-related behaviors were characterized by categorical variables for smoking (current, past, and never) and alcohol use (current, past, and never). These measures were not based on a minimum number of drinks or cigarettes per day.

Health status factors were represented by dichotomous measures (present/absent) for self-reported health conditions including coronary heart disease, congestive heart failure, stroke, diabetes, hypertension, pulmonary disease, peripheral arterial disease, self-rated health (poor/fair *vs*. good/excellent) and hearing impairment. Categorical variables were created for urinary problems (frequent leak, some, and never), and vision problems (excellent/good sight, fair sight, and poor to completely blind).[14] Measured weight and height were used to calculate body mass index (BMI) (weight (kg)/height (m^2)) which was categorized as: under/normal (BMI < 25.0); overweight (BMI: 25.0–29.9) and obese (BMI: ≥ 30.0).[15] We also controlled for any use of cardiovascular medication classes known to be associated with falls and mobility (i.e., diuretics, digoxin, and type IA antiarrhythmics).[16] In addition, we also controlled for time-varying anticholinergic medication use (defined as those agents with established muscarinic receptor affinity in vitro that also appear on a commonly accepted list of medications to be avoided in the elderly and not a psychotropic drug included in our definition of CNS medication or type IA antiarrhythmics) and a continuous variable representing the number of prescription medications (excluding those mentioned above) being taken.[17,18]

Indications for which CNS medications could be prescribed were also considered.[19] Specifically, dichotomous measures were created (present/absent) for self-reported sleep problems, anxiety, osteo-arthritis, and cancer. A categorical variable was created for bodily pain (moderate or worse, mild, and none). Time-varying dichotomous measures were created for depressive symptoms (score > 15 on Center for Epidemiologic Studies depression scale) and cognitive impairment (modified mini-mental status score < 80).[20,21]

Statistical analyses

Categorical variables were summarized by percentages and continuous variables were summarized by means (standard deviations). At baseline, 9.9% of participants had one or more missing values for covariates. For the multivariable analyses, missing covariate values were replaced with those generated using the multiple imputation (MI) procedure in SAS® software (Cary, NC). In MI, missing values of variables are simultaneously predicted using existing values of variables by modeling the joint distribution of all the covariates plus selected other

predictors. Conditional on the non-missing values for each individual, the missing values have a distribution from which several joint random samples are drawn. Each imputation dataset is analyzed separately as if there were no missing values, then the results are combined in a manner that reflects the uncertainty due to missing values. The results from five imputation datasets were combined to obtain regression coefficient estimates and confidence intervals (CIs). Bivariate Cox proportional hazards regression models were used to estimate the risk associated with individual CNS medication classes and all CNS classes combined with incident mobility limitation over 5 years.[22] Multivariable Cox proportional hazards regression was used to model combined CNS medication use and time to incident mobility limitation over 5 years.[22] CNS medication use, depression, cognitive impairment, and anticholinergic drug use were entered as time-varying variables. All other variables were fixed. Tests for duration, and dose–response were performed using multiple comparisons between multivariate adjusted hazard ratios (Adj. HRs). Underlying statistical assumptions were evaluated and verified. All statistical analyses were conducted using SAS® Version 9.1.

RESULTS

Baseline characteristics of the cohort are shown in Table 1. The mean age was 74 years and 52% were female. The overwhelming majority reported excellent/good self-rated health and eyesight. One third reported having anxiety and 8% reported sleep problems. Participants reported taking an average of six prescription medications (excluding CNS medications).

Table 2 provides information on CNS medication use by specific classes, overall and over time. At baseline 13.9% used one or more CNS medications. At baseline the most common CNS medication class used was antidepressants and the most common type was the use of selective serotonin reuptake inhibitors (72/190 or 37.89% of antidepressant users). The second most common class of CNS medications used at baseline was benzodiazepine receptor agonists. Few individuals (29/183 or 15.85%) used zolpidem and no use of zaleplon was reported. About 17% of current CNS medication users at baseline used high doses, 21.5% took two or more agents and upwards of 57% took these drugs for two or more years. All types of CNS medication use increased over the course of the study. Within 5 years after the baseline, 49.3% of participants reported incident mobility limitation.

Table 3 shows the bivariate analyses for each of the individual CNS classes and overall. As shown, all point estimates for individual classes suggest an increased risk thus supporting calculation of an overall CNS use risk estimate by combining the different CNS classes. Similar results were seen in analyses adjusting for age and gender.

Table 4 shows the bivariate, age and gender adjusted, and multivariable relationship between incident mobility limitation and CNS medication use. In multivariable models, CNS medication users compared to never users showed a higher risk for incident mobility limitation (Adj. HR 1.28; 95%CI 1.12–1.47). In addition medium or high dose and long or short duration of use of CNS medications increased the risk of incident mobility limitation compared to no use. Although there were some trends in hazard ratios, the risk of incident mobility limitation for low *versus* medium *versus* high dose or short-term *versus* long-term duration were not significantly different ($p > 0.05$) within dose or duration sub-classifications.

DISCUSSION

The combined use of CNS medications from four separate classes increased the risk of self-reported incident mobility limitation. The strengths of the current study include its size and duration of follow up, the meticulous medication coding schema, the well-defined measure of incident mobility limitations and the availability of data on numerous important cofactors.

Since simultaneous use of multiple CNS medications is common in the elderly and mobility disability is a major threat to independence and a predictor of subsequent hospitalization, and death, multiple CNS medication use may be a modifiable risk factor and a potential target for interventions to reduce mobility disability.[3,4,23]

These findings that CNS medications may impact mobility are also biologically plausible. Elders have an increased pharmacodynamic sensitivity to medications in each individual CNS medication class (i.e., benzodiazepines, antidepressants, antipsychotics, and opioids) with increased sedation, dizziness, and postural sway and falls/fractures.[24] Moreover our findings are consistent with other studies of individual CNS medication class use (i.e., benzodiazepine, antidepressants) and decline in mobility problems.[25,26] Finally, it is clinically sensible that the combined adverse effects of CNS medications could reduce physical activity and thus affect mobility.

In this study, neither dose nor duration of CNS medication use affected risk of incident mobility limitation. In a study of benzodiazepine use and loss of physical function as measured by the medical outcome study physical function scale, no dose response relationship was noted.[5] The lack of duration–response relationship suggests that the elders do not develop tolerance to the detrimental effects of CNS medication over time. Given this, clinicians when possible should avoid prescribing multiple CNS medications and discontinue these medications when possible.

The limitations of this study include the self-report nature of the primary outcome, the use of a combined CNS medication exposure predictor, potential confounding, and limits to generalizability. Since we use self-report of incident mobility limitations, we may have failed to detect an earlier stage of mobility problems that are better detected by performance measures. Such self-reported measures should be considered complementary to performance tests of mobility disability.[1,27] Questionnaire-based measures of mobility are moderately correlated with performance based measures.[28] We believe it is unlikely that any misclassification bias with the self-reported mobility measures would be differential across CNS medication user groups. Moreover, self reported incident mobility limitation is an important functional state on its own and a powerful predictor of future status.[4,26] We also lacked power to examine the multivariable impact of individual CNS medication classes since a very small proportion of our sample members (<10%) used these individual classes. As always, unmeasured factors may have confounded the findings. We controlled for numerous potential confounders, including common indications for CNS medications such as time-varying depression. Despite this it is possible that the CNS indications that were controlled for may not have adequately adjusted completely for confounding by indication. Finally, the participants in the Health ABC study were independent in mobility limitations at baseline, so these findings might not apply to more disabled older adults.

CONCLUSION

Given these findings, future studies of CNS medication reduction should include preventing mobility limitation as a potential benefit. These findings add to the growing evidence base that CNS medication exposure is risky in older adults. Clinicians should carefully evaluate a compelling need to prescribe these medications in older adults.

KEY POINTS

- CNS medication use is common in older adults.
- CNS medication use increases the risk of incident mobility limitations.

- Clinicians should consider reduction of CNS medications regardless of their dose or duration of use.

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Table 1

Characteristics of the sample at baseline (*n*=3055)

Variables	%	Mean±(SD)
Sociodemographics		
Black race	41.44	
Female gender	51.52	
Age		74.00 (2.87)
Site (Pittsburgh)	49.62	
Education		
Post secondary	42.17	
High school graduate	32.69	
<High school graduate	25.14	
Living alone	30.21	
Health-related behaviors		
Smoking status		
Current	10.36	
Past	45.80	
Never	43.84	
Alcohol use		
Current	49.49	
Past	22.26	
Never	28.25	
Health status		
Coronary heart disease	17.06	
Congestive heart disease	1.33	
Stroke	2.36	
Diabetes	15.30	
Hypertension	44.63	
Pulmonary disease	4.17	
Peripheral arterial disease	5.31	
Hearing impairment	8.77	
Excellent/good self-rated health	83.84	
Urinary problems		
No leak	61.72	
Some leak	21.45	
Frequent leak	16.83	
Vision problems		
Excellent/good sight	79.35	
Fair sight	17.87	
Poor sight to completely blind	2.78	
Body mass index (BMI)		
Underweight or normal	31.58	
(BMI<25.0)	42.66	

Variables	%	Mean±(SD)
Overweight	25.76	
(BMI: 25.0–29.9)		
Obese		
(BMI:≥30.0)		
Diuretic use	25.76	
Digoxin use	6.78	
Type IA antiarrhythmic use	0.65	
Anticholinergic use	12.73	
Number of prescription medications (excluding all the above and CNS medications)		5.95 (4.00)
Indications for central nervous system medications		
Sleep problems	8.13	
Anxiety	33.00	
Osteoarthritis	13.75	
Cancer	17.55	
Bodily pain		
None	33.68	
Mild pain	26.68	
Moderate pain or worse	39.64	
Depressive symptoms (CES-D>15)	4.75	
Cognitive impairment (modified mini-mental status<80)	10.00	

Abbreviations: CES-D=Center for Epidemiologic Studies depression scale; CNS=central nervous system; SD=standard deviation.

Table 2

Prevalence of CNS medication use and dose information over time

CNS medication use	Year 1 (*n*=3055)%	Year 2 (*n*=2911)%	Year 3 (*n*=2693)%	Year 5 (*n*=2480)%
Any CNS use	13.88	14.50	16.30	18.02
Antidepressant use	6.22	6.73	8.47	9.31
Antipsychotic use	0.72	0.72	0.89	0.89
Benzodiazepine receptor agonist use	5.99	6.05	6.13	6.73
Opioid analgesic receptor agonist use	3.73	4.12	4.49	5.00
Use of 2+ agents	2.98	3.85	4.34	4.29
High dose use (>3 SDD)	2.39	2.85	3.04	3.43
Medium dose use (1–3 SDD)	3.50	4.19	5.76	6.33
Low dose use (<1.0 SDD)	7.99	7.46	7.50	8.27
Long term use (2+ years)	7.79	10.07	11.33	11.33
Short-term use (<2 years)	6.09	4.43	4.98	6.69

Abbreviations: CNS=central nervous system; SDD=standardized daily dose.

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Table 3

Bivariate hazard ratios for self-reported incident mobility limitation by CNS medication exposure

Variables	Crude unadj. HR (95%CI)	Age–gender Adj. HR (95%CI)
Antidepressant use	1.54 (1.29, 1.84)	1.48 (1.24, 1.77)
Antipsychotic use	1.67 (1.02, 2.74)	1.55 (0.94, 2.53)
Benzodiazepine receptor agonist use	1.24 (1.01, 1.52)	1.19 (0.97, 1.46)
Opioid analgesic receptor agonist use	2.28 (1.85, 2.82)	2.21 (1.79, 2.73)
Any CNS use	1.65 (1.45, 1.88)	1.59 (1.40, 1.81)

Table 4

Multivariate hazard ratios for self-reported incident mobility limitation by time-varying CNS medication exposure

Variables	Crude unadj. HR (95%CI)	Age–gender Adj. HR (95%CI)	Fully Adj. HR (95%CI)*
Any CNS use	1.65 (1.45, 1.88)	1.59 (1.40, 1.81)	1.28 (1.12, 1.47)
No use			Reference
>3 Std dose (high)	1.76 (1.34, 2.32)	1.58 (1.33, 1.87)	1.37 (1.03, 1.81)
1-3 Std dose (medium)	1.59 (1.27, 1.99)	1.54 (1.23, 1.93)	1.34 (1.06, 1.68)
< 1 Std dose (low)	1.66 (1.39, 1.97)	1.72 (1.30, 2.26)	1.26 (0.99, 1.61)
No use			Reference
Long–term use (≥2 years)	1.56 (1.33, 1.84)	1.50 (1.27, 1.76)	1.20 (1.02, 1.42)
Short-term use (<2 years)	1.82 (1.49, 2.21)	1.76 (1.45, 2.15)	1.42 (1.16, 1.74)
No use			Reference

*Controlling for sociodemographics, health behaviors, health status, and indications for central nervous system medications.