Published in final edited form as:

J Am Geriatr Soc. 2009 February ; 57(2): 243–250. doi:10.1111/j.1532-5415.2008.02127.x.

Impact of Central Nervous System (CNS) Medication Use on Cognition Decline in Community Dwelling Older Adults: Findings from the Health, Aging and Body Composition Study

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Presented as a poster at the Gerontological Society of America 2007 Annual Meeting in San Francisco.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Studenski serves as a consultant to Merck and Co, Eli Lilly, Glaxo Smith Kline, and Asubio. Hilmer holds a patent for the Drug Burden Index, a tool for assessing risk from medication exposure in older adults.

Author Contributions: Dr. Wright assisted in the study design and the analyses, interpreted the data, and drafted the manuscript. Drs. Roumani and Boudreau assisted in the study design, acquisition of the data, and preparation of the manuscript, and performed the analyses. Dr. Newman contributed to the conception and design of the study, assisted in the acquisition of the data, and assisted in drafting the manuscript. Dr. Ruby assisted in the study design, interpretation of the data, and preparation of the manuscript. Dr. Studenski contributed to the study design and data interpretation, and assisted in the preparation of the manuscript. Drs. Shorr and Bauer contributed to the design, analyses, and interpretation of data for this study and assisted in preparing the manuscript. Drs. Simonsick and Hilmer contributed to the design of the study, interpretation of the data, and participated in the drafting of the manuscript. Dr. Hanlon conceived of and designed the study, acquired the data, participated in the analyses and interpretation of the data, and assisted in manuscript preparation.

Financial Disclosures: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. This study was specifically supported in part by NIH contracts (N01-AG-6-2101; N01-AG-6-2103; N01-AG-6-2106) and grants (R01AG027017), including the Pittsburgh Claude D. Pepper Older Americans Independence Center (P30AG024827). This study also was supported in part by a John A. Hartford Foundation Center of Excellence in Geriatrics award.

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Abstract

Objectives—To evaluate whether combined use of multiple central nervous system (CNS) medications over time is associated with cognitive change.

Design—Longitudinal cohort study.

Setting—Pittsburgh, PA and Memphis, TN.

Participants—2737 healthy adults (aged ≥ 65) enrolled in the Health, Aging and Body Composition study without baseline cognitive impairment (modified Mini-Mental Status [3MS] score >80).

Measurements—CNS medication (benzodiazepine and opioid receptor agonists, antipsychotics, antidepressants) use, duration, and dose were determined at baseline (year 1) and years 3 and 5. Cognitive function was measured with the 3MS at baseline, years 3 and 5. The outcome variables were incident cognitive impairment (3MS score <80) and cognitive decline (≥ 5 point decline on 3MS). Multivariable interval-censored survival analyses were conducted.

Results—By year 5, 7.7% had incident cognitive impairment; 25.2% demonstrated cognitive decline. CNS medication use increased from 13.9% at baseline to 15.3% and 17.1% at years 3 and 5, respectively. It was not associated with incident cognitive impairment (Adjusted Hazard Ratio [Adj. HR] 1.11; 95% Confidence Interval [CI] 0.73–1.69) but was associated with cognitive decline (Adj. HR 1.37; 95% CI 1.11–1.70). Compared to non-use, longer duration (Adj. HR 1.39, CI=1.08–1.79) and higher doses (>3 standardized daily doses) (Adj. HR 1.87; 95% CI 1.25–2.79) of CNS medications suggested greater risk of cognitive decline.

Conclusion—Combined use of CNS medications, especially at higher doses, appears to be associated with cognitive decline in older adults. Future studies must explore the effect of combined CNS medication use on vulnerable older adults.

Keywords

cognition; aged; medications

INTRODUCTION

CNS-active medications (e.g., benzodiazepines, opioids, tricyclic antidepressants, traditional antipsychotics) are commonly prescribed to older adults and represent a frequent cause of adverse medication effects, including problems with mobility, falls, and cognition in older patients.^{1–3} Medications that adversely affect cognition in particular lead to increased morbidity and health care utilization among older people.^{1–3} More importantly, CNS-medication-induced cognition problems may be reversed by adjusting or discontinuing these medications altogether.^{2, 4–6}

Few rigorously-designed observational studies have examined the cumulative risk of use of multiple classes of CNS medications on cognition function in older adults.^{2, 7, 8} Moreover, most of these studies examined use of only one class (e.g. benzodiazepines) of these medications at a time and did not include more recently available medications (e.g. benzodiazepine-receptor agonists, opioid-receptor agonists, atypical antipsychotics, and selective serotonin reuptake inhibitors (SSRIs)).^{6, 7, 9, 10} Notably, SSRIs may exert an

anticholinergic effect on cognition.² Even less is known about the potential effect of concurrent use of multiple classes of CNS-active medications on cognitive function in older people.^{11–14} Thus, the purpose of this study was to evaluate the combined effect of CNS medication use on cognitive decline and incident cognitive impairment in older community-dwelling adults. The research hypothesis was that older adults using CNS medications would have a higher risk of decline in cognitive function relative to older adults who did not use any CNS medications.

METHODS

Study Design, Sample and Source of Data

The study sample derives from a cohort of 3,075 black and white men and women aged 70–79 enrolled in the Health ABC study since 1997/98 and evaluated annually for at least 4 years.¹⁵ Sample participants represent elderly persons living in Pittsburgh and Memphis who initially reported no difficulty walking at least 1/4 mile or up a flight of stairs. This study was approved by the University of Pittsburgh and University of Tennessee Institutional Review Boards. Informed consent was obtained from each participant prior to data collection.

Data Collection and Management

Available data included detailed physiologic and performance measurements as well as questionnaire material covering socio-demographic characteristics, multiple aspects of physical health, and medication use. Participants were asked to bring to their clinic visit all medications they had taken in the previous two weeks. Trained interviewers transcribed from each medication container the following information: medication name, strength, dosage form, and whether the medication was taken routinely or as needed. The interviewer also recorded when the participant started taking the medication as well as the number of times he or she reported taking each medication the previous day, week, or month. The medication data were coded using the Iowa Drug Information System (IDIS) codes and entered into a computerized database.¹⁶ Health ABC data collection has been considered highly accurate and complete, allowing for the assessment of common confounders and outcomes.¹⁵

Study Cohort

For this investigation, the participant cohort was refined to include all Health ABC participants at the baseline interview who were cognitively intact as determined by the Modified Mini-Mental State (3MS) (described below)¹⁷ and for whom complete information medication use was obtained at baseline (n=2737). Three hundred thirty eight baseline persons were not included due to missing medication information (n=20), missing cognitive function test results (n=14) or evidence of cognitive impairment at baseline (n=304). Those who became cognitively impaired or had cognitive decline by year 3 were not included in the final year 5 models.

CNS Medication Use Exposure

Coded prescription medication data were used to define three independent variables for CNS medication use: current use, duration of use, and combined dose of CNS medication exposure. Consistent with previous studies, CNS medications were defined as those belonging to a group that together included opioid receptor agonist analgesics (IDIS class code 28080800) and other psychotropic agents (IDIS class codes 28240200 and 28160000 to 28161000) such as benzodiazepine receptor agonists, antidepressants, and antipsychotics.^{16, 18} The study group decided *a priori* to test the relationship between time-varying exposure

to CNS medications and change in cognitive function.⁷ Appendix 1 shows the individual CNS medications reported by participants and the corresponding IDIS code. Medication data and cognitive function assessments were collected at years 1, 3 and 5. Therefore, the primary independent variable was expressed as a time-varying dichotomous variable (any use versus none) at years 1, 3, and 5. At baseline, duration of use was operationally defined as either “long-term” (continuous use for previous two years) or “short-term” (use only at the baseline in-person medication review only). At follow-up years 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).

To measure dose of exposure to CNS medications, the average daily dose of each individual CNS medication was calculated by multiplying the number of doses taken the previous day by the strength of the medication. The average daily dose was then converted to a *standardized daily dose* measured in medication units. To do this, the average daily dose was divided by the minimum effective dose per day for geriatric patients recommended in a highly regarded geriatric pharmacotherapy reference.¹⁹ Thus, a person taking 1.0 standardized CNS medication unit or dose would be using the minimum recommended effective daily dose for one agent.⁷ Appendix 1 shows the minimum effective daily dose for each of the individual CNS medications with reported use by participants in this cohort. The combined CNS standardized daily dosage was operationally defined as a categorical variable based on the distribution of the data and clinical relevance. Three categories were created: lowest dose (< 1.0 standardized daily dose), moderate dose (1.0–3.0 standardized daily doses) and highest dose (>3.0 standardized daily doses).

Outcome Variables

Teng’s Modified Mini-Mental State (3MS) exam was used to operationally define two dependent variables: cognitive impairment and cognitive decline.¹⁷ The 3MS is an expanded version of the Mini-Mental State Examination with additional items testing cognitive function in the areas of memory, attention, abstract reasoning, and verbal fluency using a score of 0 to 100.¹⁷ The 3MS has high internal consistency, high inter-rater and test-retest reliability and excellent specificity and sensitivity in identifying cognitive impairment and dementia using standardized criteria and more detailed neuropsychological tests.²⁰ Moreover, a recent Health ABC study involving over 3000 participants showed that the average 3MS baseline score was 89.7 (± 0.3).²¹ In that study, the 3MS scores declined modestly from of 0.55 to 1 point per year, suggesting that a learning effect was unlikely.²¹ The 3MS was the only cognitive function measure consistently used by the Health ABC at baseline and at each followup cognition assessment. Teng’s 3MS was assessed at years 1 (baseline), 3 and 5. Incident cognitive impairment was defined as 3MS score less than 80^{20, 22–24} whereas cognitive decline was defined as a decrease in the 3MS score by 5 or more points.²¹

Covariates

To adjust for potential confounding, a number of covariates were identified that could influence the relationship between CNS medication use and change in cognitive function.^{7, 25, 26} Sociodemographic factors were represented by dichotomous variables for race, sex, study site and living alone.^{7, 9, 26–30} Age was represented as a continuous variable. Categorical variables were used to represent highest level of education achieved (post secondary education, high school graduate and less than high school graduate).³¹ A categorical variable also was created for health literacy based on reading level (ninth grade or more, seventh or eighth grade, and sixth grade or less).³² The following health-related behaviors also were characterized categorically: smoking (current, past, never) and alcohol

use (current, past, never).⁴ 31 Self-reported health was represented by dichotomous measures (present/absent) for the following health conditions: congestive heart disease, diabetes, hypertension, pulmonary disease, peripheral arterial disease, hyperlipidemia, hypothyroidism, hearing impairment, self-rated health (poor/fair vs good/excellent).⁷ 28 30 33–36 Categorical variables were created for vision problems (excellent/good sight, fair sight, poor to completely blind).³⁵ 36 The use of other medication classes known to be associated with cognitive impairment (histamine 2 receptor blockers, anticholinergics, anticonvulsants) and the mean number of prescription medications (excluding other classes separately measured) participants took were controlled for potential confounding.³¹ 37 Indications for which CNS medications could be prescribed also were considered important covariables, and dichotomous measures represented self-reported sleep problems, anxiety, painful knee osteoarthritis, cancer, and depression.⁷ 28 31 33 38 39 Anxiety was determined by responses to three items from the anxiety subscale of the validated Hopkins Symptom Checklist: 1) In the past week have you felt nervous or shaky inside? 2) During the past week have you felt tense or keyed up? 3) During the past week have you felt fearful?⁴⁰ A positive response (“yes”) to any of the three questions was operationally defined as having anxiety.⁴⁰ The presence of painful knee osteoarthritis required that participants self-report a diagnosis of degenerative arthritis or osteoarthritis in the knee made by a physician and confirmed by x-ray of the knee in addition to self-report of knee pain using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) function scale.⁴¹ This is the same approach used and validated by the Framingham Study.⁴² A categorical variable was created for bodily pain (moderate or worse, mild, none). Depression was measured by using the Center for Epidemiologic Studies Depression (CES-D) scale (positive test = score >15).⁴³ Stroke was measured by self report. Both were controlled for at baseline (year 1), and 2 (year 3) and 4 years (year 5) later.

Statistical Analyses

Categorical variables are presented as percentages, and continuous variables are summarized with means and standard deviations. The incidence of cognitive impairment, change in cognitive function, and CNS medication use, duration, and dosage were represented by percentages at each year of measurement. At baseline, 9.9% of subjects 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). Cognitive function was assessed at years 1, 3, and 5. Time-to-event for the survival analyses was the number of years from baseline to first occurrence, with censoring at year 5. To detect an association between exposure to CNS medications and incident cognitive impairment or change in cognitive function, separate multivariable interval-censored survival analyses were conducted while adjusting for demographics, health-related behaviors, health status, and indications for CNS medications.^{44–46} CNS medication use, stroke and depression were entered as time-varying variables. All other variables were fixed. In separate models, hazard-ratios and 95% confidence intervals for each of the primary independent variables were computed after adjusting for all the covariates and baseline cognitive function. The underlying statistical assumptions of the model were evaluated and verified. All statistical analyses were conducted in SAS[®] Version 9.1 (Cary, NC).

RESULTS

Table 1 shows the characteristics of the cohort at baseline. The mean age was 73.6 (SD ± 2.9), and nearly half were women. Eighty percent had graduated from high school, over half had ever smoked, and half reported current alcohol use. At least 80% reported good or excellent vision and self-rated health. One-third reported problems with anxiety while less

than 5% had evidence of depression. Ten percent indicated difficulty sleeping, and two-thirds reported some pain. Study participants took an average of six prescription medications (excluding CNS-active medications).

Table 2 shows the prevalence of individual classes and overall CNS medication use and exposure over time. At baseline (year 1), 13.9% of subjects used at least one CNS-active medication. At years 3 and 5, the prevalence had increased to 15.3% and 17.1%, respectively. Antidepressants were used more commonly than any other CNS medication class. SSRIs were the most commonly used type of antidepressant. Two thirds of those who took CNS-active medications (10.7% overall) were long term (≥ 2 years) users. Among those who took CNS medications, nearly 18% were taking high doses (>3 standardized daily doses) at years 3 and 5 of the study.

By year 5, 9.9% of participants had 3MS scores that dropped below 80 (i.e. cognitive impairment (Table 3). Approximately 1/4 of participants by year 5 had demonstrated incident cognitive decline (5 point decline on the 3MS).

Any CNS-active medication use, compared to non-use, was associated with cognitive decline (Adjusted [Adj.] Hazard Ratio [HR] 1.37; 95% Confidence Interval [CI]= 1.11–1.70) (Table 4). Of note, SSRI use alone showed a trend towards an increased risk of cognitive decline (Adj. HR 1.27; 95% CI 0.90–1.81). The standardized, or combined, daily dose of CNS medications used was the strongest predictor of cognitive decline. “Highest” doses (> 3 SDD) of CNS medications were more strongly associated with cognitive decline (Adj. HR 1.87; 95% CI=1.25–2.79). However, “lowest” and “moderate” doses of CNS medication use were not statistically associated with cognitive decline. Both short and long term use were also associated with cognitive decline, but only the association with long term use was statistically significant. Similar, but non-significant ($p>0.05$) associations were found between any exposure, duration of exposure, and combined dose of exposure to CNS-active medications and incident cognitive impairment. Notably, SSRI use alone also showed a trend towards an increased risk of cognitive impairment (Adj. HR 1.44; 95% CI 0.75–2.77).

DISCUSSION

This longitudinal cohort study demonstrated an association between the combined use of CNS medications, especially at high doses, and an increased risk of clinically important cognitive decline. This relationship was detected in a large sample of healthy, community dwelling older persons even after controlling for a number of potentially confounding factors that also could have affected central nervous system function. Furthermore, both short and long duration of CNS medication use were associated with a 5 point decline on the 3MS, a clinically important cognitive decline. These findings were consistent with a study examining the risk of these CNS medication use variables on another common geriatric syndrome, recurrent falls.⁴⁷

These findings also were consistent with the findings of studies of single classes of CNS-active medications that demonstrated an association between medication use and cognitive decline.^{2, 3, 6, 7, 9, 10} For example, Pomaro et al, and Hanlon et al, found that higher doses of benzodiazepines were associated with cognitive decline while lower doses were not.^{7, 10} Marcantonio et al, found that higher doses of certain opioid analgesics, specifically meperidine, were associated with delirium⁹ while another study showed that immediate release opioids were more likely to be associated with cognitive decline than delayed release opioids.⁴⁸ A few studies have attributed decline in cognitive function to antidepressant and antipsychotic use because of their anticholinergic and sedative properties.^{2, 5} The analyses

in the current study encompassed the (combined) use of all of these classes of CNS medications.

This study has several noteworthy implications. First, these findings should not be interpreted as suggesting that the treatment of pain or psychiatric symptoms should be avoided because of the risk of cognitive impairment, especially since these conditions are often under-treated. A study by Morrison et al., showed that the risk of delirium was more pronounced in those with severe pain as opposed to the use of opioids.⁴⁹ Similarly, the use of tricyclic antidepressants for depression has been associated with positive, negative, and a lack of effects on cognitive function.^{50, 51} It is conceivable that different agents within the same major class of medications (e.g., antidepressants) may affect cognitive function differently. However, it is interesting to note in the current study that both SSRI use and tricyclic antidepressant use demonstrated similar risks to cognitive function. Ultimately, the practical implications of this study suggest that clinicians should use the lowest possible combined doses of CNS-active medications, particularly when treating concurrent pain and psychiatric conditions, in order to minimize the risk of cognitive decline. Further research may be able to identify specific combined dosing thresholds beyond which the incidence of adverse effects on cognitive function dramatically and unacceptably increases. As a second noteworthy implication, these findings reiterate the possibility that a *reversible* component to cognitive decline may exist in the presence of excessive dosing of CNS-active medications. Further research may elucidate this possibility. Third, the question of whether CNS-active medication use in healthy older adults is associated with incident cognitive impairment has not been satisfactorily answered, and other larger studies are needed to explore this.

This study has several potential limitations. First, the measure of cognitive function, the 3MS, was not as sensitive to change as a full battery of neuropsychological tests (e.g., visual reproduction test, trails B, verbal fluency, word list recall) would be.^{24, 52, 53} However, psychometric testing of the 3MS has demonstrated its reliability between raters and its ability to approximate in studies estimates of the actual incidence of mild cognitive impairment separately from dementia.²⁰ Secondly, medication use information was limited to that collected at three points in time. Nonetheless, one of the strengths of medication data collection in the Health ABC study is that it is based upon participants' actual medication use rather than a clinician's record of medications prescribed to participants or pharmacy dispensing. A third limitation is that given the low incidence of cognitive impairment (as measured by the dichotomous 3MS measure), the power to detect any association with CNS medication use was limited. For example, post-hoc calculations revealed that this study had 9.1% power to detect the magnitude of the association between higher (> 3 SDD) doses of CNS medications and cognitive impairment. However, it is important to note that the hazard ratio for both the risk of developing cognitive decline and impairment with the use of "highest" doses of CNS medication were nearly identical. Therefore, this point estimate is probably the best first approximation of the true magnitude of the association between higher CNS medication doses and cognitive impairment. As an additional limitation, potential confounding by indication attributable to behavioral complications that sometimes occur in older adults with severe cognitive impairment (i.e. dementia) could not be controlled for as this information was not collected by the Health ABC study. Finally, this study sample included at baseline only relatively healthy community dwelling older adults living in two states and, therefore, may not be representative of other populations elsewhere.

Conclusion

This is one of the first studies to explore the relationship between the combined dose of CNS-active medication use across multiple classes (i.e., benzodiazepines, antidepressants,

antipsychotics, and opioids) and cognitive decline in healthy community-dwelling older people. This study confirms a strong association between highest combined daily dose of CNS medication use and cognitive decline. Future studies should explore and compare the effect of combined CNS medication use on more vulnerable (e.g., those living in a long term care facility) older adults.

Acknowledgments

Funding Support: NIH contracts (N01-AG-6-2101; N01-AG-6-2103; N01-AG-6-2106) and grants R01AG027017 and P30AG024827 and the John A. Hartford Foundation Center of Excellence in Geriatrics.

Sponsors' Roles: The organizations that funded this study did not influence the interpretation of the data or the development of this manuscript.

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Table 1

Characteristics of the Sample at Baseline (n=2737).

Variables	%	Mean +/- (SD)
<u>Sociodemographics</u>		
Black Race	36.8	
Female Gender	52.5	
Age		73.58 ± 2.85
Site (Pittsburgh)	51.0	
Education		
Post secondary	45.9	
High school graduate	34.0	
< High school	20.1	
Health Literacy		
Ninth grade or more	67.7	
Seventh or eight grade	12.1	
Sixth grade or less	20.2	
Living alone	30.4	
<u>Health-Related Behaviors</u>		
Smoking Status		
Current	9.4	
Past	46.7	
Never	43.9	
Alcohol Use		
Current	51.0	
Past	21.0	
Never	28.0	
<u>Health Status</u>		
Congestive Heart Disease	2.7	
Stroke	2.2	
Diabetes	14.7	
Hypertension	44.8	
Pulmonary Disease	4.1	
Peripheral Arterial Disease	7.7	
Hyperlipidemia	14.8	
Hypothyroid	12.1	
Fair/Poor Self-rated health	14.1	
H2 blocker use	10.9	
Anticholinergic use	13.1	
Anticonvulsant use	1.5	
Number of prescription drugs (excluding the above)		6.06 ± 3.98
Hearing Impairment	8.6	
Vision problems		

Variables	%	Mean +/- (SD)
Excellent/Good sight	80.9	
Fair sight	16.8	
Poor to completely blind	2.4	
Indications for Central Nervous System Medications		
Sleep problems	10.9	
Anxiety	33.5	
<u>Knee</u> osteoarthritis	14.6	
Cancer	17.6	
Bodily Pain		
None	33.7	
Mild pain	25.6	
Moderate pain or worse	39.6	
Depression	4.5	

Table 2

Prevalence, Duration, and Dose of Current CNS Medication Use.

CNS Medication Use	Year 1 (n=2737) N (%)	Year 3 (n=2284) N (%)	Year 5 (n=1907) N (%)
Antidepressant Use	168 (6.14)	179 (7.84)	163 (8.54)
Selective Serotonin Reuptake Inhibitors	72 (2.63)	95 (4.16)	108 (5.66)
Tricyclics	73 (2.67)	49 (2.15)	29 (1.52)
Other agents	23 (0.84)	35 (1.53)	26 (1.36)
Antipsychotic Use (Any)	19 (0.69)	13 (0.57)	13 (0.68)
Conventional	15 (0.55)	11 (0.48)	5 (0.26)
Atypical	4 (0.15)	2 (0.09)	8 (0.42)
Benzodiazepine receptor agonist use	166 (6.07)	134 (5.87)	127 (6.66)
Opioid Analgesic Receptor Agonist Use	95 (3.47)	95 (4.16)	84 (4.40)
Any Current Use	373 (13.6)	349 (15.3)	326 (17.1)
Short-term use (< 2 years)	155 (5.7)	105 (4.5)	124 (6.5)
Long-term use (≥ 2 years)	218 (7.9)	244 (10.7)	202 (10.6)
Lowest dose use (<1.0 SDD)	211 (7.7)	163 (7.1)	147 (7.7)
Moderate dose use (1–3 SDD)	97 (3.5)	124 (5.5)	118 (6.2)
Highest dose use (> 3 SDD)	65 (2.4)	62 (2.7)	61 (3.2)

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

Table 3

Incident Change in Cognitive Function Over Time.

Measure of Cognitive Function Change Using 3MS	Year 1 to Year 3 n=2284 (%)	Year 3 to Year 5 n=1629 (%)
Incident Cognitive Impairment	143 (6.3)	68 (3.6)
3MS score < 80		
Incident Cognitive Decline	464 (20.3)	227 (13.9)
≥5 point decrease		

Table 4

Multivariable Relationship Between CNS Medication Use and Cognitive Change Measured by the 3MS.*

CNS Medication Use	3MS < 80	≥ 5 point decrease in 3MS
	Adj. HR (95% CI)	Adj. HR (95% CI)
No Exposure	reference	Reference
Any Exposure	1.11 (0.73–1.69)	1.37 (1.11–1.70) [†]
Short Term use (< 2 yrs)	1.08 (0.61–1.92)	1.34 (0.97–1.86)
Long Term Use (≥ 2 yrs)	1.13 (0.66–1.96)	1.39 (1.08–1.79) [†]
Lowest dose use (<1.0 SDD)	0.62 (0.30–1.28)	1.29 (0.96–1.74)
Moderate dose use (1–3 SDD)	1.37 (0.77–2.44)	1.27 (0.92–1.75)
Highest dose use (> 3 SDD)	1.87 (0.91–3.83)	1.87 (1.25–2.79) [†]

Abbreviations: CNS=central nervous system; Adj=adjusted; HR=Hazard Ratio; CI=confidence interval

* Multivariable interval censored survival analyses adjusted for sociodemographic, health behavior, health status factors and indications for CNS medications.

[†] p < 0.05

Appendix 1

Central Nervous System Medications Taken by Health ABC Study Participants Years One Through Five.

IDIS Code *	Medication Class/Medication Name	Minimum Effective Daily Dose (mg) *
<i>Selective Serotonin Reuptake Inhibitor Antidepressants</i>		
28160701	Fluoxetine	10
28160703	Sertraline	25
28160704	Fluvoxamine	100
28160705	Citalopram	10
28160711	Escitalopram	5
28160702	Paroxetine	10
<i>Tricyclic Antidepressants</i>		
28160601	Amitriptyline	10
28160602	Imipramine	10
28160681	Doxepin	10
28160650	Trimipramine	25
28160688	Clomipramine	25
28160689	Desipramine	10
28160695	Nortriptyline	10
<i>Other Antidepressants</i>		
28160486	Nefazodone	200
28160458	Venlafaxine	50
28160415	Trazodone	25
28160434	Bupropion	150
28160617	Mirtazepine	15
<i>Conventional Antipsychotics</i>		
56220089	Chlorpromazine	10
28160858	Loxapine	20
28160906	Fluphenazine	1
28160909	Perphenazine	2
28160912	Thioridazine	10
28160913	Trifluoperazine	0.5
28161014	Haloperidol	0.25
28160804	Chlorprothixene	75
<i>Atypical Antipsychotics</i>		
28160836	Olanzapine	2.5
28160834	Quetiapine	150
28160822	Risperidone	0.25
28160844	Ziprasidone	40
<i>Opioid Receptor Agonist Analgesics</i>		
28080818	Methadone	5
28080819	Morphine	15
28080840	Propoxyphene Hydrochloride	260

IDIS Code *	Medication Class/Medication Name	Minimum Effective Daily Dose (mg) *
28080840	Propoxyphene Napsylate	400
28080854	Tramadol	200
28080883	Oxycodone	10
48000072	Hydrocodone	10
48000063	Codeine	60
28080892	Pentazocine	300
28080810	Fentanyl (transdermal)	25mcg/hr
28080818	Methadone	5
<i>Benzodiazepine Receptor Agonists</i>		
28240202	Chlordiazepoxide	15
28240205	Diazepam	4
28240206	Flurazepam	15
28240212	Clonazepam	0.5
28240215	Oxazepam	30
28240216	Estazolam	0.5
28240222	Triazolam	0.125
28240228	Clorazepate	15
28240231	Temazepam	15
28240232	Alprazolam	0.75
28240276	Lorazepam	2
28240834	Zolpidem	5
28240856	Zaleplon	5

Abbreviations: IDIS=Iowa Drug Information System; mg=milligrams

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