Cumulative Anticholinergic Exposure Is Associated with Poor Memory and Executive Function in Older Men

Ling Han, MD, PhD, Joseph V. Agostini, MD,*† and Heather G. Allore, PhD**

OBJECTIVES: To examine the longitudinal relationship between cumulative exposure to anticholinergic medications and memory and executive function in older men.

DESIGN: Prospective cohort study.

SETTING: A Department of Veterans Affairs primary care clinic.

PARTICIPANTS: Five hundred forty-four community-dwelling men aged 65 and older with diagnosed hypertension.

MEASUREMENTS: The outcomes were measured using the Hopkins Verbal Recall Test (HVRT) for short-term memory and the instrumental activity of daily living (IADL) scale for executive function at baseline and during follow-up. Anticholinergic medication use was ascertained using participants' primary care visit records and quantified as total anticholinergic burden using a clinician-rated anticholinergic score.

RESULTS: Cumulative exposure to anticholinergic medications over the preceding 12 months was associated with poorer performance on the HVRT and IADLs. On average, a 1-unit increase in the total anticholinergic burden per 3 months was associated with a 0.32-point (95% confidence interval (CI) = 0.05–0.58) and 0.10-point (95% CI = 0.04–0.17) decrease in the HVRT and IADLs, respectively, independent of other potential risk factors for cognitive impairment, including age, education, cognitive and physical function, comorbidities, and severity of hypertension. The association was attenuated but remained statistically significant with memory (0.29, 95% CI = 0.01–0.56) and executive function (0.08, 95% CI = 0.02–0.15) after further adjustment for concomitant non-anticholinergic medications.

CONCLUSION: Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect verbal memory and executive function in older men. Prescription of drugs with anticholinergic effects in older persons deserves continued attention to avoid deleterious adverse effects. **J Am Geriatr Soc 56:2203–2210, 2008.**

Key words: anticholinergic score; medication use; cognitive test; cohort study; older men; polypharmacy

Adverse drug effects represent a formidable challenge for clinicians and caregivers of older persons.[1–4] Greater risk of cognitive impairment,[1,2] falls,[3] and functional decline[4,5] have been observed in older persons exposed to a variety of prescription and over-the-counter medications. With the increasing trend of drug consumption with age, identifying and preventing adverse drugs effects in older persons has important public health implications.

Although the causes of adverse drug effects are multifaceted, it has been suspected that the anticholinergic properties of medications play an important role in drug-induced cognitive and functional impairment.[1,2,5–7] Induction of experimental delirium, an acute cognitive disorder, by administration of anticholinergic drugs has been reported in humans and shown to be reversed by a cholinergic agonist.[8–10] Elderly patients may be more vulnerable to anticholinergic insult because of aging-related changes in pharmacokinetics and pharmacodynamics, including diminished function of cholinergic brain receptors, greater permeability of the blood—brain barrier, and slower metabolism and drug elimination.[6,7,11] Moreover, older persons often take several medications simultaneously to treat different comorbidities (so-called polypharmacy),[12,13] of which more than one may have anticholinergic effects. For example, an estimated 30% or more of older nursing home residents take two or more anticholinergic medications;[6,14,15] and in the general population, this figure could exceed 50%.[15] Therefore, older persons are at greater risk of developing anticholinergic drug-induced adverse effects.

Several population-based epidemiological studies have demonstrated a cross-sectional or short-term association between anticholinergic medication use and cognitive[15–17] or functional[4,5,17] impairment. More recently, a study of

From the *Program on Aging, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; and †Clinical Epidemiology Research Center, Department of Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut.

Address correspondence to Ling Han, MD, PhD, Yale University Department of Internal Medicine, Program on Aging, 300 George Street Suite 775, New Haven, CT 06511. E-mail: ling.han@yale.edu

DOI: 10.1111/j.1532-5415.2008.02009.x

0002-8614/08/$15.00

372 older persons in France found that continuous users of anticholinergic medications over 1 year had poorer performance than nonusers on several cognitive tests, including nonverbal memory and visuospatial construction.[18] To the knowledge of the authors of the current study, that was the first community-based prospective cohort study that demonstrated evidence for adverse effects of chronic anticholinergic use over 1 year on cognitive outcomes in older persons. However, in that study the anticholinergic use was defined as two mutually exclusive states (users vs nonusers) and was ascertained only at the start and the end of the 1-year follow-up.[18] Potential cumulative effects of the anticholinergic exposure across medications over the course of follow-up was not evaluated. In addition, given the increasing trend of polypharmacy with age,[12–14] whether and to what degree the observed anticholinergic effects may be attributable to other concomitantly used non-anticholinergic medications requires clarification. Another report of chronic anticholinergic effect on cognitive function of older persons was derived in a clinical sample of 69 patients with Alzheimer's disease treated with cholinesterase inhibitors.[19] Even under continuous cognitive-enhancing therapy, those with concomitant anticholinergic medications showed greater cognitive decline at 2 years than those not exposed to such medications.[19]

Given the established link between acute anticholinergic toxicity and cognitive impairment and the lack of literature addressing chronic anticholinergic effects in older persons, the current study was purposed to examine the longitudinal relationship between cumulative anticholinergic exposure and cognitive performance of community-dwelling older adults over a 2-year follow-up period. It was hypothesized that cumulative anticholinergic exposure over time, across medications with different level of anticholinergic potency, might adversely affect the performance of older persons on memory and executive tasks, independent of other risk factors for cognitive and functional impairment. The secondary objective was to evaluate the specificity of a clinicians' consensus-based measure of total anticholinergic burden in predicting memory and executive dysfunction beyond the effects of concomitant medications.

METHODS

Participants

The study used data from the *Connecticut Veterans Longitudinal Cohort*, consisting of 767 veterans aged 65 and older recruited at a Department of Veterans Affairs (VA) primary care clinic between July 2000 and August 2001. The Yale University School of Medicine and VA Connecticut institutional review boards approved the study; the protocol and recruitment process have been described previously.[20] Data collected included demographic information, neuropsychological tests, activities of daily living (ADLs), physical performance tests, and clinical conditions, including vital signs, comorbidities, medication regimens, and health habits. In 2005, a second wave of data collection was added in a subset of the cohort with a diagnosis of hypertension at study entry. For each 3-month quarter over the 2-year follow-up period, a research assistant with medical training reviewed the primary care visits of these participants with hypertension. The entire medication regimen (prescribed and nonprescribed) was abstracted. For this study, the study population was restricted to the 544 men with diagnosed hypertension, a common clinical condition that requires chronic pharmacological treatment and typically involves treatment with multiple medications.[21]

OUTCOME MEASURES

The outcome measures for this study focused on two major domains: short-term memory and executive ability. The short-term memory was measured using the Hopkins Verbal Recall Test (HVRT),[22,23] which consists of three trials of immediate free recall of 12 words, with scores ranging from 0 (worst) to 36 (best). Executive function was measured using the instrumental activity of daily living (IADL) scale of the Older American Resources and Services (OARS) instrument,[24] which assesses ability to perform such tasks as handling money, using the telephone, and preparing meals, with scores ranging from 0 (complete dependence) to 7 (complete independence). Trained research personnel administered the two tests following a standardized protocol, first at baseline and then at 1- and 2-year follow-up. Although short-term memory represents a core area of cognitive function known to be specific to dementia pathology and anticholinergic toxicity,[8,9] executive performance requires competence in cognitive and physical function and hence is vulnerable to the adverse drug effects on cholinergic and potentially noncholinergic neurotransmitting pathways.[1,4–6,11]

Measure of Anticholinergic and Other Medications

A clinician-rated anticholinergic score was used to quantify potential anticholinergic effects of each study medication.[25] The clinician-rated anticholinergic score was an ordinal scale originally developed to assess potential effects of anticholinergic medication use on severity of delirium symptoms in older medical patients, with scores ranging from 0 (no effect) to 3 (strong effect). The rating procedure and resultant anticholinergic drug list have been previously reported.[25] Previous clinical epidemiological and pharmacological studies demonstrated that this clinical consensus-based rating scale has good concurrent criterion validity against other lists of anticholinergic medications and serum anticholinergic activities (SAAs)[25–30] and predictive validity against measures of cognitive impairment.[25,28]

To apply the clinician-rated anticholinergic scale, two authors (JA and LH) reviewed a complete list of the generic medications used in the current study cohort. Medications were assigned an existing anticholinergic score if one was available from the original anticholinergic drug list (n = 164). For medications without an available score, their therapeutic classifications were reviewed based on the American Hospital Formulary Service system.[31] Classes judged to have no anticholinergic effect as a whole, such as antibiotics, antineoplastic agents, hematological drugs, diagnostic agents, expectorants, ophthalmic and nasal preparations, dietary supplements, and vitamins, were assigned a 0 score (n = 204). For the remaining unrated medications (n = 80), three geriatricians (JA, LW, and CF) conducted an independent rating. The median value of the three ratings was adopted as the final anticholinergic score for each medication, following the original protocol.[25]

The exposure time window was defined as the 12 months preceding each follow-up assessment at 1 and 2 years. Because of lack of data on duration of medication use, an overall sum of anticholinergic scores across medications over the four quarters was calculated, under an assumption that a recorded medication was used for all the days during that quarter. To facilitate clinical interpretation of regression parameters for anticholinergic exposure, the overall sum was divided by 4 as an index for cumulative anticholinergic exposure intensity, or total anticholinergic burden, on a 3-month time unit. In addition, when number of medications per patient, rather than cumulative intensity over time, is of interest, an average of the 4 quarters provides the most compatible estimates to compare with previous investigations that typically collected data at a single time point.

Following the same approach, cumulative number of antihypertensive, psychotropic and total non-anticholinergic medications was calculated on a 3-month time unit for each year as an index for concomitant medication exposure. Antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, diuretics, and centrally acting agents, were chosen because they were prescribed to the majority of the cohort members. In addition, previous studies have reported potential cognitive effects of antihypertensive drugs, although the results remain inconsistent or conflicting, suggesting a potentially detrimental (e.g., beta-blockers), neutral, or protective (e.g., diuretics) effect.[1,32,33] Psychotropic medications, including antidepressants, benzodiazepines, and other hypnotic-sedatives, anxiolytics, antipsychotics, antiparkinsonian agents, and anticonvulsants, have been associated with a variety of drug-induced cognitive or functional impairments.[1,2,16,17,34] Apart from other centrally active pharmacological mechanisms, many psychotropic drugs and several antihypertensive agents also have documented anticholinergic properties in vivo or in vitro.[1,6,7,26,30] In previous studies, such dual-action medications were typically analyzed as if they were exclusively anticholinergic.[5,16–18] To reflect clinical reality and to avoid potential overestimation of anticholinergic effect in multivariable modeling (see Statistical Analyses section for details), an antihypertensive or psychotropic drug that was rated as having anticholinergic properties was retained in each group rather than counted solely as anticholinergic. Finally, total non-anticholinergic medication burden was computed by including all the drugs with a clinician-rated anticholinergic score of 0, to represent maximal possible confounding effects of concomitant medications.

A list of study medications that are considered to have anticholinergic effects, along with their assigned anticholinergic scores, is provided in Appendix A.

MEASURES OF COVARIATES

Data on potential confounders of the putative association between anticholinergic exposure and cognitive impairment were collected through interview with patients at baseline or review of medical records. Demographic factors included age, education (years), race (white vs other), and living arrangement (alone vs with others) before enrollment. Health—behavioral factors included history of alcohol use and smoking and depressive symptoms, as measured using the 11-item, self-reported Center for Epidemiologic Studies Depression Scale (CES-D).[35] ADL function was assessed on the seven basic items from the OARS.[24] Medical conditions were obtained from participants' medical records and were used to define the Charlson Comorbidity Index, a global measure of the severity and multiplicity of comorbid diseases.[36] The severity of hypertension was rated on a 5-level ordinal scale ranging from 0 to 4, with 0 indicating normal blood pressure (i.e., systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg) and 4 indicating severe hypertension (i.e., systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), corresponding generally to blood pressure stages as classified by national guidelines.[21] Use of a global and a specific measure of clinical comorbidities addressed the need to control for confounding by drug indications.[37]

STATISTICAL ANALYSES

Baseline characteristics of the study population and longitudinal distribution of the outcome measures and medication use during follow-up were described using means and standard deviations or frequencies and proportions, as appropriate. The bivariate association between cumulative medication exposure and each outcome was assessed using Spearman correlation coefficients (r_s).

A mixed-effects linear regression model was used to examine the hypothesized association between cumulative anticholinergic exposure and performance on the HVRT and IADLs. Because there were only two repeated outcome measures per subject, and there was no prior knowledge regarding the trends of their variance and covariance over time, an "unstructured" covariance structure was adopted to account for potential interdependence of the repeated measures over time on the same participants.[38]

The effect of cumulative anticholinergic exposure was sequentially adjusted for the a priori selected covariates. The baseline model included only the time-dependent cumulative anticholinergic exposure as the sole predictor (Model 1). Then demographic variables (age, race, education, and living arrangement) were introduced into the model (Model 2). To account for heterogeneity of participants' cognition at study entry, the baseline value of the HVRT and IADL measures were included. Next, the models were adjusted for health behavioral factors: tobacco and alcohol use, depression symptoms, and ADL function (Model 3). Finally, Charlson Comorbidity Index and severity of hypertension were added as potential indications for prescribing multiple medications in general and for prescribing antihypertensive medications in particular (Model 4). Potential departures of the estimated anticholinergic effect from linearity and homogeneity over time were tested by adding a quadratic term and interaction with follow-up year, respectively.

Sensitivity analyses were performed to assess the robustness of the primary mixed-effect models. Because a few highly anticholinergic medications (e.g., tricyclic antidepressants) were primarily indicated for treating mental conditions, to ensure that the specific group of anticholinergic medications or their indication diseases did not determine the observed association, the final models were refit by excluding participants with a diagnosis of depression, posttraumatic stress disorder, anxiety, or alcohol abuse or dependence based on medical records. In addition, because 4.3% to 19.5% of

surviving participants were missing an outcome measure at the first or second annual follow-up, multiple imputation analyses were conducted to assess potential bias of the final models due to missing data using the SAS MI and MIANALYZE procedure (SAS Institute, Inc., Cary, NC).

Previous epidemiological studies have largely ignored potential confounding by co-medications when evaluating effects of anticholinergic drugs. To address this important methodological concern and to examine the specificity of anticholinergic medications, exploratory analyses were conducted by adjusting the final models for different measures of concomitant medication use as an additional time-dependent covariate (Table 4), namely antihypertensive (Model 4.1), psychotropic (Model 4.2), and total non-anticholinergic medication burden (Model 4.3) The *t* statistic derived from significance tests of individual parameter estimates was employed as an effect size index for comparing the strength of the anticholinergic exposure in predicting a specific outcome with that of different measures of concomitant medications.[39] The former two models may result in an overadjustment due to potential collinearity between anticholinergic burden and concomitant antihypertensive or psychotropic medication use, but they reduce the risk of type I error. In contrast, the third model eliminated potential collinearity and confounding from all non-anticholinergic medications but may be subject to potential misclassification by clinician rating.

To provide insight into the biological mechanism of observed cumulative anticholinergic effects, number of (3-month) quarters in which a participant used anticholinergic medications (range 0–4) was counted as a surrogate for duration of anticholinergic use, and its linear and curvilinear relationship with the outcomes was tested. In addition, because prior evidence for anticholinergic drug—induced cognitive impairment was primarily established over an "acute" exposure time window, typically in hours or days after the drug intake,[7,10,11] the final model was refit by confining anticholinergic exposure to the most recent quarters.

Statistical analyses were conducted using SAS software version 9.1 (SAS Institute Inc.). Model fit was assessed using the likelihood ratio test that evaluates the difference of the nested models against a chi-square distribution with a degree of freedom equaling the number of added covariates.[38] The hypotheses were tested at a two-sided significance level of .05.

RESULTS

The baseline characteristics of the study population are summarized in Table 1. The cohort comprised relatively healthy older men, with the majority being functionally independent. Their hypertension severity was mild to moderate. Three hundred forty-two (62.9%) participants were using anticholinergic medications, with a mean anticholinergic score of 1.3 ± 1.5 (median 1.0). On average, the cohort members were taking 2.3 ± 1.2 antihypertensive medications (median 2.0), 1.5 ± 1.3 psychotropic medications (median 1.0), and 6.4 ± 3.1 non-anticholinergic medications (median 6.0). The most frequently used medications with moderate to strong anticholinergic effects (a clinician-rated anticholinergic score of 2 or 3) were ranitidine (9.6%), amitriptyline (2.8%), fexofenadine (2.2%), nortriptyline (1.8%), and paroxetine (1.1%). During the follow-up period, 364 (66.9%) and 378 (69.5%) participants used at least one anticholinergic medications during the first or second year of follow-up, respectively. Of them, the majority (57.1% and 56.6%) used these medications for 3 or 4 quarters, and another 23.1% and 27.8% used them for 2 quarters each year. Fewer than 20% used these drugs in only 1 quarter.

Table 1. Characteristics of the Study Population at Baseline (N = 544)

Characteristic	Value
Age, mean ± SD	74.4 ± 5.2
Race, n (%)	
White	483 (88.8)
Nonwhite	61 (11.2)
Living arrangement before enrollment, n (%)	
Alone	157 (29.1)
Other	383 (70.9)
Education, years, mean ± SD	12.0 ± 2.8
Current smoker, n (%)	
Yes	447 (82.2)
No	97 (17.8)
Alcohol use, n (%)	
Current	174 (32.0)
Past	109 (20.0)
Never	261 (48.0)
Center for Epidemiological Studies Depression Scale score, mean ± SD*	3.9 ± 3.7
Activity of daily living score, mean ± SD†	6.9 ± 0.4
Charlson Comorbidity Index, mean ± SD	1.5 ± 1.4
Level of hypertension, n (%)	
1 (normal, SBP < 120 mmHg and DBP < 80 mmHg)	78 (14.4)
2 (SBP 120–139 mmHg or DBP 80–89 mmHg)	302 (55.6)
3 (SBP 140–159 mmHg or DBP 90–99 mmHg)	133 (24.5)
4 (SBP ≥160 mmHg or DBP ≥100 mmHg)	30 (5.5)
Number of anticholinergic drugs used, n (%)‡	
0	202 (37.1)
1	219 (40.3)
2	92 (16.9)
3	31 (5.6)
Total anticholinergic score across drugs, mean ± SD	1.3 ± 1.5
Number of antihypertensive drugs used, mean ± SD§	2.3 ± 1.2
Number of psychotropic drugs used, mean ± SD§	1.5 ± 1.3
Total number of non-anticholinergic drugs used, mean ± SD#	6.4 ± 3.1
Hopkins Verbal Recall Test score, mean ± SD‖	14.8 ± 4.5
Instrumental activity of daily living score, mean ± SD**	6.5 ± 1.0

Note: Participants with missing data were excluded from calculating the percentages and means.

* Range 0–33; higher scores indicate greater symptomatic severity.

† Range 0–7; higher scores indicate greater independence.

‡ Based on a clinician-rated anticholinergic score (range 0–3; higher score indicating greater anticholinergic potency) > 0.

§ Drugs in these two groups may also have anticholinergic effects based on the clinician-rated anticholinergic score.

Included only the drugs that have a clinician-rated anticholinergic score of 0.

‖ Range 0–36; higher scores indicate better memory.

** Range 0–7; higher scores indicate greater independence.

SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 2. Memory and Executive Function in Users and Nonusers of Anticholinergic Medications

		Anticholinergic User*			Anticholinergic Nonuser		
Time of Assessment	Function	n	Mean ± SD	Median	n	Mean ± SD	Median
Baseline	HVRT†	341	14.7 ± 4.4	14.0	202	15.1 ± 4.6	15.0
	IADL‡	342	6.4 ± 1.0	7.0	202	6.6 ± 0.9	7.0
Year 1	HVRT	344	14.8 ± 5.2	15.0	163	15.5 ± 5.1	15.0
	IADL	345	6.1 ± 1.4	7.0	163	6.4 ± 1.1	7.0
Year 2	HVRT	309	16.4 ± 6.0	16.0	103	16.9 ± 6.4	16.0
	IADL	332	6.0 ± 1.5	7.0	119	6.6 ± 0.9	7.0

* Participants who used at least one medication with a clinician-rated anticholinergic score (range 0–3) >0 at baseline or during the specified follow-up period.
† Hopkins Verbal Recall Test (HVRT) scores range from 0 to 36, with higher scores indicating better memory.
‡ Instrumental activity of daily living (IADL) scores range from 0 to 7, with higher scores indicating greater independence.
SD = standard deviation.

Thirteen (2.4%) and 19 (3.6%) participants died during the first or second year of follow-up, respectively. The memory and executive function of the study cohort at baseline and during the follow-up in survivors are shown in Table 2. At each assessment occasion, participants who were users of anticholinergic drugs appeared to perform worse than nonusers, although the cross-sectional difference between the two groups was statistically significant only on the IADL (*t*-test, $P = .02$ to .001) and not the HVRT (*t*-test, $P = .17$ to .45).

Table 3 summarizes the results of the series of mixed-effects regression models on the two outcomes, adjusting for other potential risk factors. There was an independent association between cumulative anticholinergic exposure and poorer performance on the HVRT and IADLs after adjusting for demographic factors (Model 2), health behavioral factors (Model 3), and potential indications for prescribing (Model 4). There were no statistically significant nonlinear effects or interactions with follow-up time (all $P > .10$, data not shown).

Exclusion of participants with a psychiatric diagnosis (n = 120) from the final models resulted in no substantive changes in the estimated decremental effect for cumulative anticholinergic exposure on HVRT (0.39, 95% CI = 0.06–0.71, $P = .02$) or IADLs (0.14, 95% CI = 0.06–0.21, $P < .001$). Multiple imputations analyses derived consistent conclusion (data available upon request).

Table 4 summarizes exploratory analyses of the final models (Model 4 of Table 3) after taking into account concomitant medication use. The effect of cumulative anticholinergic exposure was attenuated but remained statistically significant after adjusting for cumulative number of antihypertensive (Model 4.1) and non-anticholinergic medications (Model 4.3) but not psychotropic medications (Model 4.2). Based on the ratio of their *t* statistics, the anticholinergic medications had a consistently stronger effect than antihypertensive, psychotropic, and total non-anticholinergic medications in predicting HVRT.

Table 3. Association Between Cumulative Anticholinergic Exposure and Memory and Executive Function in 544 Men with Hypertension

	Hopkins Verbal Recall Test	Instrumental Activities of Daily Living
Model	Effect Estimate* (95% Confidence Interval)	*P*-Value
1†	0.30 (−0.02–0.61)	.06 / 0.16 (0.11–0.25)	<.001
2‡	0.42 (0.17–0.67)	.001 / 0.15 (0.09–0.21)	<.001
3§	0.36 (0.10–0.61)	.007 / 0.12 (0.06–0.18)	<.001
4‖	0.32 (0.05–0.58)	.02 / 0.10 (0.04–0.17)	.001

* Effect estimate using a mixed-effects linear regression model representing expected decrement in the score of each outcome associated with 1-unit increase in the cumulative anticholinergic exposure per 3 months.
† Included the cumulative anticholinergic exposure as a sole predictor.
‡ Adjusted the cumulative anticholinergic exposure for age, race, education, living arrangement before enrollment, follow-up year, and baseline value of the outcome.
§ Included all the variables in Model 2, plus Center for Epidemiologic Studies-Depression scale score (range 0–63), activity of daily living score (range 0–7), and tobacco and alcohol use at baseline.
‖ Included all variables in Model 3 plus Charlson Comorbidity Index and level of hypertension at baseline.

Anticholinergic medication effects were stronger than antihypertensive and total non-anticholinergic medications, but not psychotropic medications, in predicting IADL scores.

Refitting the final models by using number of exposed quarters (instead of cumulative anticholinergic exposure over four quarters) as a predictor and by confining anti-

Table 4. Association Between Cumulative Anticholinergic Exposure and Memory and Executive Function Adjusted for Concomitant Medications and Other Risk Factors

	Hopkins Verbal Recall Test	Instrumental Activities of Daily Living
Model*	Effect Estimate† (95% Confidence Interval) *P*-Value; *t* Ratio‡	
4.1	0.28 (0.01–0.55) .04; 2.3	0.10 (0.04–0.17) .002; 158.0
4.2	0.25 (−0.06–0.57) .12; 2.3	0.06 (−0.02–0.13) .13; 0.7
4.3	0.29 (0.01–0.56) .04; 2.9	0.08 (0.02–0.15) .01; 1.3

* All of the models adjusted for the same set of covariates as Model 4 of Table 3, including age, race, education, living arrangement before enrollment, Center for Epidemiologic Studies-Depression Scale (range 0–63) score, activity of daily living score, tobacco and alcohol use, Charlson Comorbidity Index, level of hypertension, follow-up year, and baseline value of the outcome. In addition, Model 4.1 adjusted for total concomitant antihypertensive medications, which included some anticholinergic drugs; Model 4.2 adjusted for total concomitant psychotropic medications, which included some anticholinergic drugs; and Model 4.3 adjusted for total concomitant non-anticholinergic medications, which included only the non-anticholinergic drugs based on a clinician-rated anticholinergic score of 0.
† Effect estimate using a mixed-effects linear regression model representing expected decrement in the score of each outcome associated with 1-unit increase in the cumulative anticholinergic exposure per 3 months.
‡ A ratio of the *t* statistics for the effect of anticholinergic exposure to that of the concomitant medications adjusted in each model (see above), with a value greater than 1 indicating that the anticholinergic exposure has a stronger association with the outcome.

cholinergic exposure to the last quarter yielded consistent results. One additional quarter of anticholinergic use was associated with a 0.21-point (95% CI = 0.01–0.42, $P = .04$) and 0.05-point (95% CI = 0.00–0.10 $P = .05$) decrease in the HVRT and IADL scores, whereas the corresponding estimates for a 1-unit increase in the "acute" anticholinergic exposure were 0.12 (95% CI = −0.07–0.32 $P = .23$) on HVRT and 0.10 (95% CI = 0.06–0.15, $P < .001$) on IADLs.

DISCUSSION

In this cohort of community-living older men with diagnosed hypertension, total anticholinergic burden across medications used over 1 year was significantly associated with poor performance on memory and executive tasks during the 2-year follow-up period. This association remained statistically significant after control for other potential risk factors for cognitive and functional impairment, including age, education, ADL function, comorbidities, severity of hypertension, and concomitant use of non-anticholinergic medications, including antihypertensives and psychotropics. To put these findings in a clinical context, an older community-dwelling man with hypertension, whose total anticholinergic burden is one unit (population mean) per 3 months (or equivalently, four units per 12 months) is expected to have 0.30- and 0.10-point deficits on the memory and executive tasks, respectively, based on the clinician-rated anticholinergic score. The adverse anticholinergic effect on the two tasks would be approximately 3 and 1 times as great as the combined effects of non-anticholinergic drugs. These results suggest that chronic use of medications with even low to moderate anticholinergic effects may represent an independent risk factor for memory and executive dysfunction in older persons.[18,19]

The current study largely supports findings from several large-scale population-based studies. One study reported that continuous use of anticholinergic medications over 1 year was independently associated with poorer performance on attention, short-term memory, and visuospatial construction,[18] although the association with immediate verbal recall (and implicit memory) lost statistical significance after adjusting for age. In contrast, the current study demonstrated a strong and consistent linear relationship between poorer verbal recall and greater cumulative anticholinergic exposure, independent of an array of identified risk factors for cognitive impairment and disease indications for prescribing. Other population studies have also found similar relationships between anticholinergics and functional impairment in older adults but over a much shorter exposure time window or using a cross-sectional design. For instance, a previous study found that use of anticholinergic drugs in the previous 2 weeks was associated with poorer visual memory, verbal fluency, and global cognitive function.[16] Similarly, it has been observed that users of anticholinergic medication in the previous 2 weeks performed significantly worse than nonusers on ADL and IADL scales and muscle strength measures.[5]

In comparison with the previous studies, the methodological advantages of the current study included the ascertainment of medication use during the course of follow-up, defining anticholinergic use as a cumulative exposure, and controlling for confounding by indications. In addition, the relationship was assessed using a longitudinal, repeated-measures regression model, which allows simultaneous adjustment for baseline (e.g., age and education) and time-varying (e.g., concomitant medication use) confounders and has greater statistical power due to the use of more than one observation from each subject. The anticholinergic effect remains statistically significant after adjusting for total concomitant non-anticholinergic or antihypertensive burden and has a stronger association than both. Its association with memory dysfunction also appears to be stronger than that of concomitant psychotropic medications, despite the potential collinearity between the anticholinergic and psychotropic medications. These findings provide preliminary evidence for the specificity of the cumulative anticholinergic effect on cognitive function, which has not been examined longitudinally in previous studies. Nevertheless, the weaker (and nonsignificant) anticholinergic effect than that of psychotropic medications on executive dysfunction may suggest that drug-induced executive impairment, unlike memory dysfunction, may involve other neurotransmitting mechanisms than anticholinergicity alone[4,6,17,30] and hence may be more strongly correlated with an overall measure of centrally active drug burden than specific anticholinergic exposure.

In light of the well-established acute anticholinergic toxicity syndrome,[7–10] the associations noted here may arise from long-term cumulative anticholinergic insult over time. Most medications that the older adults in the current study were taking have only mild to moderate anticholinergic effects, and the dosages taken may not be considered to be extremely high. Nevertheless, previous studies have shown that, even at low level of SAA, such medications (e.g., atenolol and ranitidine) could cause cognitive and functional deficits in elderly people.[7,15,26] Therefore, their long-term use may repeatedly cause subthreshold, and probably reversible, damage to the central nervous system and thereby gradually reduce the accuracy, efficiency, and speed of some cognitive abilities. Older persons may be more vulnerable to such cumulative anticholinergic insults, not only because they are subject to age-related oversensitivity to and reduced metabolism of anticholinergic medications,[6,11] but also because they often chronically use more than one medication with anticholinergic effects.[1,15,26] If such a "cumulative insult" mechanism exists, then a single theorem that, at lower or subthreshold levels, anticholinergic exposure requires a longer time to "cause" cognitive impairment could explain the statistically insignificant "acute" anticholinergic effect and significant "dose" effect of the exposure duration on memory function.

This study had several limitations. First, the measures of medication use were based on data abstracted from VA primary care medical records and did not take into account prescriptions from non-VA sources or dosage and actual duration of medication use. Second, the clinician-rated anticholinergic score is based on physicians' clinical judgment rather than explicit external criteria and hence may not accurately reflect the pharmacological profile or SAA level of the medications.[17,29] For instance, ranitidine may not have "moderate" anticholinergic properties, as it was rated here. Similarly, homatropine-containing eye drops have been associated with anticholinergic delirium, and ophthalmic preparations should be ascertained as part of

regular medication reviews. Third, study outcomes were measured in their original, quantitative units, which avoided arbitrary dichotomization and improved statistical power but also added uncertainty about the clinical significance of the detected functional deficits. Fourth, unmeasured and imprecisely measured risk factors, such as physical inactivity and specific medical and psychiatric conditions, may have introduced residual confounding or could offer an alternative explanation for the observed associations. Finally, the study population was restricted to relatively healthy men who had regular medical access and a shared comorbidity (hypertension). Whether these findings can be generalized to the aging population at large requires further investigation.

In summary, in this cohort of community-dwelling older men with hypertension, cumulative anticholinergic exposure across medications used over 1 year was associated with poorer performance on short-term verbal memory and executive function. Age, education, cognitive and physical function at baseline, comorbid diseases, severity of hypertension, and concomitant medications did not explain this association. In addition, the effect of cumulative anticholinergic exposure on memory dysfunction appeared to be stronger than antihypertensive, psychotropic, and total non-anticholinergic medications. Future epidemiological studies should take into account the dose and duration of actual use of the medications and replicate these findings in women and other older adult populations without restriction to specific comorbidity. Clinicians prescribing drugs with anticholinergic effects should pay close attention to potential adverse effects that may arise with long-term use of these drugs in older persons.

ACKNOWLEDGMENTS

We thank Lisa Walke, MD, and Carlos Fragoso, MD, for help with rating the anticholinergic score; Gregory Acampora, MD, and Gail McAvay, PhD, for assistance with data abstraction or management; and M. Carrington Reid, MD, PhD, for assembling the original patient cohort. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Financial Disclosure: This study was supported in part by the Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine (P30AG21342) from the National Institute on Aging. Dr. Agostini was also supported by a VA Health Services Research Career Development Award.

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 manuscript.

Author Contributions: The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors participated in the study design, drafting and critical revision of the manuscript, interpretation of the results, and approved the final version for submission. In addition, JA participated in obtaining funding, data acquisition, review and classification of the medications, and rating of the anticholinergic score. LH developed the protocol for the anticholinergic score and the study, designed and implemented the data analyses, and wrote the manuscript. HA supervised the statistical analyses.

Sponsor's Role: The funding sources and sponsor had no involvement in the study design, data collection, analysis, or interpretation.

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APPENDIX A

Table A1. List of Potential Anticholinergic Medications Evaluated in the Study Based on Clinician-Rated Anticholinergic Score

Generic Drug	Clinician-Rated Anticholinergic Score
Alprazolam	1
Amitriptyline	3
Atenolol	1
Atropine	3
Baclofen	2
Belladonna	3
Benazepril	1
Betaxolol	1
Bupropion	1
Carbamazepine	1
Carbidopa	1
Cetirizine	2
Chlordiazepoxide	1
Chlorpheniramine	3
Chlorpromazine	3
Codeine	1
Cyclobenzaprine	1
Desipramine	2
Dextromethorphan	1
Diazepam	1
Diphenhydramine	3
Doxepin	3
Fexofenadine	2
Fluoxetine	1
Guaifenesin	1
Homatropine	3
Hydrocodone	2
Imipramine	3
Ketorolac	1
Loperamide	1
Loratadine	1
Methadone	2
Methocarbamol	1
Metoprolol	1
Morphine	1
Nefazodone	1
Nortriptyline	3
Olanzapine	1
Oxycodone	1
Paroxetine	2
Perphenazine	2
Phenobarbital	1
Prochlorperazine	2
Propantheline	2
Propoxyphene	2
Quetiapine	2
Ranitidine	2
Reglan	3
Risperidone	1
Robitussin	1
Scopolamine	3
Sertraline	1
Thioridazine	3
Tolterodine	3
Tramadol	2
Trandolapril	1
Trazodone	1
Triazolam	1
Trihexyphenidyl	3
Venlafaxine	1

(*Continued*)

Table A1. (Contd.)