Drugs With Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population

The 3-City Study

Isabelle Carrière, PhD; Annie Fourrier-Reglat, PhD; Jean-François Dartigues, MD; Olivier Rouaud, MD; Florence Pasquier, MD; Karen Ritchie, PhD; Marie-Laure Ancelin, PhD

Background: Despite the high intake of medications with anticholinergic properties by community-dwelling elderly persons, the effects on cognitive decline and dementia have rarely been evaluated.

Methods: Participants were 4128 women and 2784 men 65 years or older from a population-based cohort recruited from 3 French cities. Cognitive performance, clinical diagnosis of dementia, and anticholinergic use were evaluated at baseline and 2 and 4 years later.

Results: A total of 7.5% of the participants reported anticholinergic drug use at baseline. Multivariate-adjusted logistic regression indicated that women reporting use of anticholinergic drugs at baseline showed greater decline over 4 years in verbal fluency scores (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.11-1.79) and in global cognitive functioning (OR, 1.22; 95% CI, 0.96-1.55) than women not using anticholinergic drugs. In men, an association was found with decline in visual memory (OR, 1.63; 95% CI, 1.08-2.47) and to a lesser extent in executive function (OR, 1.47; 95% CI, 0.89-2.44). Notable interactions were observed in women between anticholinergic use and age, apolipoprotein E, or hormone therapy. A 1.4- to 2-fold higher risk of cognitive decline was observed for those who continuously used anticholinergic drugs but not for those who had discontinued use. The risk of incident dementia over the 4-year follow-up period was also increased in continuous users (hazard ratio [HR], 1.65; 95% CI, 1.00-2.73) but not in those who discontinued the use of anticholinergic drugs (HR, 1.28; 95% CI, 0.59-2.76).

Conclusions: Elderly people taking anticholinergic drugs were at increased risk for cognitive decline and dementia. Discontinuing anticholinergic treatment was associated with a decreased risk. Physicians should carefully consider prescription of anticholinergic drugs in elderly people, especially in the very elderly and in persons at high genetic risk for cognitive disorder.

Arch Intern Med. 2009;169(14):1317-1324

Author Affiliations: Inserm, U888, Université Montpellier 1, Montpellier, France (Drs Carrière, Ritchie, and Ancelin); Inserm, U657 (Dr Fourrier-Reglat), and Inserm, U897 (Dr Dartigues), Université Bordeaux 2, Bordeaux, France; Department of Neurology, Centre Hospitalier Universitaire Dijon, Dijon, France (Dr Rouaud); and Department of Neurology, Centre Hospitalier Universitaire Lille, Lille, France (Dr Pasquier).

In the absence of an effective clinical treatment for age-related neurodegenerative disorder, research has focused on the identification of potential risk factors in order to delay cognitive decline and prolong autonomy. Reversible drug-induced cognitive impairment has been described in clinical studies of patients with cognitive impairment or neuropsychiatric disorder. They have generally focused on acute (single-dose) or short-term administration of anticholinergic medication and delirium.[1] Few community studies have, however, been undertaken despite the relatively high intake of over-the-counter and prescription drugs consumed by elderly patients.[2] Several cross-sectional studies in elderly persons have demonstrated a link between anticholinergic medication and global cognitive functioning,[3-6] psychomotor speed,[7,8] visual and declarative memory,[4] and implicit learning.[7] The causal relationship between long-term use of anticholinergics and subclinical cognitive decline thus remains unclear owing to the scarcity of longitudinal population studies. In a retrospective study of 592 older adults, Bottiggi et al[9] observed an accelerated decline over a 6-year period of psychomotor speed and executive functioning in anticholinergic users. In a sample of 372 elderly participants, we previously reported[10] an important association between continuous anticholinergic use for 1 year and poorer performance on specific cognitive domains. Most important, anticholinergic drug use was observed to be a strong predictor of mild cognitive impairment (MCI), although the risk of subsequent dementia could not be estimated owing to small numbers of patients with dementia. Very recently, in a cohort of 544 community-dwelling older

men with hypertension, cumulative anticholinergic exposure was shown to be associated with poor performance on verbal memory over 2 years.[11]

Surprisingly, to our knowledge, previous studies have not examined genetic vulnerability, although 2 small randomized controlled trials (RCTs)[12,13] suggested increased cognitive sensitivity in participants with an allele producing the ε4 type of apolipoprotein E (*APOE*E4*) shortly after acute anticholinergic administration. Sex differences have also not been considered, although different risk profiles for both MCI and progression to dementia have been reported between men and women.[14] Finally, there is some evidence that short-term estrogen pretreatment may attenuate anticholinergic-induced cholinergic dysfunction,[15,16] suggesting possible protective effects of hormone therapy (HT). This hypothesis has yet to be tested.

Thus, although there is accumulating evidence to suggest that anticholinergics may increase the risk of cognitive decline and dementia, this hypothesis remains to be tested within a large prospective study that is able to take into account multiple independent and interactive causes of cognitive decline. To our knowledge, the possible reversible effect on cognitive functioning of stopping anticholinergic treatment has also never been evaluated. Our aim was to examine the relationship over time between anticholinergic use and cognitive decline and onset of dementia in community-dwelling elderly persons, taking into account sex and genetic vulnerability.

METHODS

STUDY POPULATION

Participants were recruited as part of a multisite cohort study of community-dwelling persons 65 years or older from the electoral rolls of 3 French cities from 1999 to 2001.[17] The study protocol was approved by the ethics committee of the University-Hospital of Bicêtre (France), and written informed consent was obtained from each participant. The participants were followed up after 2 years and 4 years. Of the 9077 dementia-free participants included in the cohort, 363 died, 631 were lost to follow-up, and 1171 did not have repeated cognitive testing or had missing data for at least 1 baseline adjustment variable. The present analyses were conducted for 6912 participants. Of these, 914 participants (13.2%) had only 1 follow-up examination. The mean (SD) duration of follow-up was 3.5 (0.6) years. Participants not included in the present analysis were more frequently female, were older, had a lower education level, more frequently used anticholinergics, and had lower baseline cognitive scores (data not shown). There were 59.7% of women in the sample. The mean (SD) age was 73.6 (5.3) years for men and 73.8 (5.2) years for women.

COGNITIVE OUTCOME MEASURES

A battery of cognitive tests assessed different areas of cognitive functioning. The Isaacs Set Test[18] provided a measure of verbal fluency or semantic access that is sensitive to changes in both frontal and temporal areas. Participants were asked to generate as many words as possible within a given semantic category (animals, colors, fruits, and cities) in a limited time. Fluency was assessed as the total score corresponding to the sum of the number of words generated in each category within 30 seconds (Isaacs total retrieval), as well as the number of words reported for the first (early retrieval) and the second 15-second interval (late retrieval). The Benton Visual Retention Test (BVRT)[19] assessed visual memory; psychomotor speed and executive function were assessed with the Trail Making Tests A and B, respectively (TMT A and TMT B),[20] and the Mini-Mental State Examination (MMSE) was used as a global measure of cognitive function.[21] All of the cognitive tests were administered at baseline, and during 2- and 4-year follow-ups of the follow-up, except the TMT A and TMT B, which were not given in the 2-year follow-up. Consequently, the analysis based on these tasks involves only 5716 participants. Cognitive decline was defined as being in the lowest quintile of the difference between baseline score and either follow-up visit (after 2 or 4 years), except for TMT for which the highest quintile of the difference was considered.[22]

DIAGNOSIS OF DEMENTIA

A preliminary diagnosis and classification of dementia at each follow-up examination was made by the local clinical investigators for the 3C Study according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) revised criteria,[23] and validated by a national panel of neurologists independently of the 3C investigators. The date of onset of dementia was the date of the follow-up interview when dementia was diagnosed.

ANTICHOLINERGIC DRUG USE

An inventory of all drugs (prescription and over-the-counter drugs) used during the preceding month was included in a standardized interview. Medical prescriptions and, where feasible, the medications themselves were checked by the interviewer. Reported medicines were coded according to the World Health Organization's Anatomical Therapeutic Chemical Classification.[24] The list of drugs with anticholinergic properties was established from the Thériaque,[25] the Banque de Données Automatisée sur les Médicaments (BIAM),[26] and VIDAL classifications.[27]

SOCIODEMOGRAPHIC AND CLINICAL VARIABLES

The standardized interview included questions on demographic characteristics, education level, marital status (married, widowed, single, or divorced), mobility, height, and weight. Information was obtained on alcohol consumption, tobacco use, caffeine consumption, and HT for women. History of stroke, angina pectoris, myocardial infarction, and cardiovascular surgery was established according to standardized questions with additional information where necessary from general practitioners. Recent asthma crisis, hypertension, hypercholesterolemia, and diabetes mellitus were also recorded. Depressive symptoms were assessed by the Center for Epidemiological Studies–Depression Scale (CES-D)[28] with a cutoff point of 16 on a scale of 60. Fasting blood samples were taken for cholesterol levels, and apolipoprotein E genotyping was performed as described previously.[22]

STATISTICAL ANALYSIS

We used univariate and multivariate logistic regression analyses to determine if baseline consumption of anticholinergic drugs was associated with the odds of cognitive decline. Men and women were examined in separate analyses because they differed in both anticholinergic drug use and profiles of cogni-

tive ability. The χ^2 test was used to identify sex-related differences. After sex stratification, univariate odds ratios (ORs) were adjusted for center, age, educational level, and baseline cognitive performance (model 0). Multivariate-adjusted logistic regression included covariates that were associated with cognitive decline ($P<.15$). Model 1 was adjusted for center; age; education; baseline cognitive performance; body mass index (BMI); alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; apolipoprotein E; diabetes mellitus; asthma; and HT for women. Compared with model 1, model 2 was further adjusted for diseases associated with anticholinergic drug use to take into account a possible prescription bias (eg, depression, ischemic diseases, Parkinson disease, and hypertension).

A Cox model with delayed entry was used in the analysis of dementia incidence taking age as the basic timescale and birth as the time origin.[29] This analysis was undertaken with 7123 participants without missing data for baseline adjustment variables but with possibly missing repeated cognitive testing. The analyses were not stratified by sex to allow full adjustment despite relatively small numbers of incident cases. The full model was adjusted for sex; center; education; BMI; alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; apolipoprotein E; diabetes mellitus; asthma; depression; ischemic diseases; Parkinson disease; and hypertension. Analyses were performed using SAS statistical software (version 9.1; SAS Inc, Cary, North Carolina).

RESULTS

POPULATION CHARACTERISTICS

Within this elderly, community-dwelling population, 520 of the 6912 participants (7.5%) were taking anticholinergic drugs at baseline, of whom 36 participants (6.9%) were taking 2 anticholinergic drugs simultaneously, and 8 (1.5%) were taking 3 drugs. The main classes for these drugs consisted of antidepressants (1.9%), digestive antispasmodics (1.6%), genital-urinary antispasmodics (1.3%), H_1 antihistaminics (1.0%), anxiolytics (0.9%), cardiovascular medications (0.5%), antiepileptics (0.5%), antipsychotics (0.3%), antiasthmatics (0.1%), and anti-Parkinson drugs (0.1%) (eTable, http://www.archinternmed.com). None of the participants reported use of cholinesterase inhibitors.

Overall, women reported anticholinergic drug use more often than men (9.6% vs 4.4%, respectively; $P<.001$). Men and women were found to differ in all other characteristics at baseline except the presence of *APOE*E4*. They also differed in baseline cognitive performance, with a higher proportion of women showing low scores on the MMSE, BVRT, and TMT A and TMT B (data not shown).

The cross-sectional associations of baseline covariables with anticholinergic use were evaluated after stratification by sex. For both men and women, anticholinergic use was higher in participants with depression ($P<.001$), in those with low alcohol consumption ($P=.02$ in women and $P=.001$ in men), and with poor mobility ($P=.03$ in women and $P<.001$ in men) (**Table 1**). Women not consuming caffeine ($P=.008$) or with diabetes mellitus ($P=.007$), ischemic diseases ($P=.02$), or Parkinson disease ($P<.001$) were more frequent anticholinergic drug users.

ASSOCIATIONS BETWEEN ANTICHOLINERGICS AND COGNITIVE DECLINE OVER A 4-YEAR FOLLOW-UP

In the longitudinal logistic regression analyses, decline in cognitive performance was defined as a decrease from baseline of at least 6 points on the Isaacs Set Test total score or at least 2 points on the BVRT and the MMSE (lowest quintiles). For the TMT, cognitive decline was defined as an increase from baseline of at least 16 (TMT A) or 35 seconds (TMT B) (**Table 2**). In women, univariate logistic regression adjusted for age, educational level, center, and baseline cognitive score (model 0) indicated a significant association between anticholinergic use and decline in Isaacs Set Test total score (OR, 1.47; 95% confidence interval [CI], 1.16-1.86; $P=.002$) and in the MMSE (OR, 1.26; 95% CI, 1.00-1.60; $P=.05$). No significant association was observed for the BVRT ($P=.33$) and the TMT A ($P=.73$) or TMT B ($P=.88$). In men, anticholinergic use was significantly associated with decline in the BVRT (OR, 1.70; 95% CI, 1.13-2.56; $P=.01$) but was not significantly associated in the TMT B (OR, 1.61; 95% CI, 0.98-2.64; $P=.06$) in the Isaacs Set Test or the TMT A. In multivariate logistic regression (model 1), the same associations were observed with significant cognitive decline in the Isaacs Set Test in women ($P=.003$) and in the BVRT in men ($P=.01$). These associations persisted in the complete model (model 2) further adjusted for other confounders such as disease associated with anticholinergic prescription (depression, ischemic diseases, Parkinson disease, and hypertension). The OR was 1.41 (95% CI, 1.11-1.79; $P=.006$) for decline on the Isaacs Set Test total score in women. This effect seemed related to the early retrieval phase (OR, 1.27; 95% CI, 0.99-1.62; $P=.06$), whereas no notable association was found for the late retrieval phase (data not shown). In men, the OR was 1.63 (95% CI, 1.08-2.47; $P=.02$) for decline in the BVRT test. However, the association with decline in the TMT B in men was not significant in model 2 ($P=.14$), as well as for the MMSE in women ($P=.10$). For women specifically, an interaction was observed on the MMSE between anticholinergic use and age (risk increasing with age; $P=.002$) and apolipoprotein E (the risk being significantly increased only for *APOE*E4* carriers; OR, 2.05; 95% CI, 1.24-3.40; $P=.005$ vs OR, 1.07; 95% CI, 0.81-1.40; $P=.65$ in non–*APOE*E4* carriers). There was also an interaction between anticholinergic use and HT on early retrieval on the Isaacs Set Test; the risk of cognitive decline in those using anticholinergics was increased for those who had never used HT (OR, 1.44; 95% CI, 1.07-1.94; $P=.02$) in contrast with current HT users (OR, 0.51; 95% CI, 0.25-1.05; $P=.07$).

COGNITIVE DECLINE ACCORDING TO THE PATTERN OF ANTICHOLINERGIC DRUG USE DURING FOLLOW-UP

A total of 5969 participants (86.4%) did not report anticholinergic drug use at baseline or at the later follow-up examinations, 175 (2.5%) reported anticholinergic use only at baseline but not at either the 2- or 4-year follow-up (hereinafter, discontinuing group), and 319 (4.6%) reported

Table 1. Characteristics of the Study Population as a Function of Anticholinergic (ACH) Drug Use at Baseline

Characteristic	Women Prescribed ACH Drugs, %			Men Prescribed ACH Drugs, %		
	No (n=3731)	Yes (n=397)	*P* Value	No (n=2661)	Yes (n=123)	*P* Value
Age, y						
65-69	25.5	23.2		26.4	19.5	
70-74	33.1	30.5	.30	35.0	34.1	.25
75-80	27.7	30.5		24.6	28.5	
>80	13.7	15.8		14.0	17.9	
Education, y						
5	24.6	27.7		21.4	30.1	
9	40.2	41.3	.11	30.0	33.3	.004
12	21.0	20.9		19.5	22.0	
>12	14.2	10.1		29.1	14.6	
CES-D ≥16	26.4	42.3	<.001	13.0	27.6	<.001
Ischemic diseases[a]	11.5	15.4	.02	22.1	23.6	.70
BMI						
Normal	53.9	51.9		38.1	35.8	
Overweight	32.8	34.5	.73	49.2	50.4	.85
Obese	13.3	13.6		12.7	13.8	
Diabetes mellitus[b]	6.3	9.8	.01	12.7	17.1	.15
Asthma[c]	2.2	2.5	.65	1.3	2.4	.29
Hypertension[d]	53.5	50.9	.32	59.9	64.2	.34
Parkinson disease	0.6	2.3	<.001	1.3	3.3	.07
Hypercholesterolemia[e]	67.9	70.0	.39	83.5	82.9	.88
Alcohol intake, g/d						
0	26.4	32.8		7.8	13.0	
1-36	72.0	66.2	.02	72.6	79.7	<.001
>36	1.6	1.0		19.6	7.3	
Smoking						
Never	81.1	83.4		30.2	26.8	
Former	15.2	13.1	.51	61.7	64.2	.72
Current	3.7	3.5		8.1	9.0	
Caffeine intake per day, units[f]						
0-1	23.9	31.0		27.4	26.8	
>1-3	59.4	54.2	.01	59.3	60.2	.98
>3	16.7	14.8		13.3	13.0	
Mobility						
Confined to home	1.7	2.5		1.0	3.3	
Confined to neighborhood	4.1	6.6	.03	1.8	6.5	<.001
Not confined	94.2	90.9		97.2	90.2	
HT						
Current	14.9	16.9				
Former	16.8	16.1	.57			
Never	68.3	67.0				
*APOE*E4*	19.0	19.7	.77	20.7	17.1	.32
MMSE score < 26	15.2	17.9	.15	11.5	15.5	.18
IST total score[g] <40	19.7	24.2	.03	20.1	22.8	.47
BVRT[g] <11	29.6	40.1	<.001	22.8	40.7	<.001
TMT A[f] >69[h]	18.0	25.8	<.001	13.9	21.7	.04
TMT B[f] >139[h]	18.7	27.0	<.001	15.9	25.0	.02

Abbreviations: *APOE*E4*, allele producing the ε4 type of apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BVRT, Benton Visual Retention Test; CES-D, Center for Epidemiological Studies–Depression Scale; HT, hormone therapy; IST, Isaac Set Test; MMSE, Mini-Mental State Examination; TMT, Trail Making Test.

[a] History of stroke, myocardial infarction, angina pectoris, or arteritis.

[b] Diabetes mellitus defined as glucose level of at least 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or treated.

[c] Asthma crisis over the past year.

[d] Systolic blood pressure (BP) of 160 mm Hg or higher or diastolic BP of 95 mm Hg or higher or intake of antihypertensive drugs.

[e] Total cholesterol level of at least 239.4 mg/dL (to convert to nanomoles per liter, multiply by 0.0259) or treated by lipid-lowering agents.

[f] One unit equals 100 mg of caffeine.

[g] Percentage of participants with lowest cognitive performances at baseline (lowest quintile)

[h] The numbers of female participants who had the TMT tests were 3125 non–ACH users and 322 users, and the numbers of male patients were 2177 non–ACH users and 92 users (see the "Methods" section for details).

anticholinergic drug use both at baseline and at least at the 2-year examination (hereinafter, continuing group), of whom 204 were also users at the 4-year follow-up. Other participants who reported the intermittent use of anticholinergics during the follow-up (n=449) were not considered in the following analyses.

Table 2. Baseline Anticholinergic Use and Cognitive Decline Over the 4-Year Follow-up Period[a]

	Model 0		Model 1		Model 2	
Cognitive Decline Score	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Women (n=4128)[b]						
ΔIST total ≤ −6	1.47 (1.16-1.86)	.002	1.44 (1.13-1.83)	.003	1.41 (1.11-1.79)	.006
ΔBVRT ≤ −2	1.13 (0.89-1.43)	.33	NA	NA	NA	NA
ΔTMT A ≥ 16	1.05 (0.78-1.42)	.73	NA	NA	NA	NA
ΔTMT B ≥ 35	0.98 (0.73-1.31)	.88	NA	NA	NA	NA
ΔMMSE ≤ −2	1.26 (1.00-1.60)	.05	1.25 (0.99-1.58)	.07	1.22 (0.96-1.55)	.10
Men (n=2784)[b]						
ΔIST total ≤ −6	1.03 (0.67-1.59)	.89	NA	NA		NA
ΔBVRT ≤ −2	1.70 (1.13-2.56)	.01	1.68 (1.11-2.53)	.01	1.63 (1.08-2.47)	.02
ΔTMT A ≥ 16	0.84 (0.48-1.46)	.53	NA	NA	NA	NA
ΔTMT B ≥ 35	1.61 (0.98-2.64)	.06	1.58 (0.96-2.62)	.07	1.47 (0.89-2.44)	.14
ΔMMSE ≤ −2	1.39 (0.92-2.09)	.12	NA	NA	NA	NA

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; IST, Isaac Set Test; MMSE, Mini-Mental State Examination; NA, not applicable; OR, odds ratio; TMT, Trail Making Test.

[a] Model 0 was adjusted for center, age, education, and baseline cognitive performance. Model 1 was adjusted for center; age; education; baseline cognitive performance; body mass index; alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; *APOE*E4* (allele producing the ε4 type of apolipoprotein E); diabetes mellitus; and asthma (for men and women) as well as hormone therapy for women. Model 2 was adjusted for all the covariates in model 1, plus depression, ischemic diseases, Parkinson disease, and hypertension (for men and women).

[b] Except for TMT, which concerned 3447 women and 2269 men.

Compared with women who had never reported the use of anticholinergic drugs, women in the continuous group were at higher risk of cognitive decline on the Isaacs Set Test in fully adjusted models (OR, 1.46; 95% CI, 1.08-1.98; *P*=.02) and on the MMSE (OR, 1.42; 95% CI, 1.06-1.90; *P*=.02) (**Table 3**). The same pattern was observed for men in the continuous group in relation to decline in the BVRT test (OR, 1.94; 95% CI, 1.15-3.27; *P*=.01) and the TMT B (OR, 1.94; 95% CI, 1.06-3.58; *P*=.03). However, the risk was not modified for participants who had discontinued the use of anticholinergic drugs.

ASSOCIATIONS BETWEEN BASELINE ANTICHOLINERGIC DRUG USE AND 4-YEAR INCIDENCE OF DEMENTIA

Among the 7123 participants included in the analysis concerning dementia outcome, there were 221 newly diagnosed cases during follow-up, of whom 143 patients had Alzheimer disease. In the subsample from which intermittent users were excluded, a multiadjusted delayed-entry Cox model showed an increased risk for incident dementia or Alzheimer disease for persons who had used anticholinergic drugs continuously (hazard ratio [HR], 1.65; 95% CI, 1.00-2.73; *P*=.05; and HR, 1.94; 95% CI, 1.01-3.72; *P*=.05, respectively) but not for those who had discontinued anticholinergic treatment after the inclusion (**Table 4**).

COMMENT

In this large prospective study, 7.5% of these community-dwelling elderly persons reported taking anticholinergics. Our results indicate an increased risk in cognitive decline and dementia, which remained significant after adjustment for the other multiple possible codeterminants of cognitive decline (see Table 2 and Table 4 for *P* values). It is worth noting that similar results were obtained in the unadjusted model (model 1) and in the model that adjusted for the diseases associated with anticholinergic treatment (model 2). This suggests that the anticholinergic drugs themselves rather than the underlying burden of illness is the likely cause of the cognitive decline. Further supporting a causative effect of the anticholinergic medications, we found that the cognitive decline seemed reversible after anticholinergic treatment was discontinued. This could at least partly account for the reversible dementia observed in some patients with MCI.[30,31]

ASSOCIATION BETWEEN ANTICHOLINERGICS AND COGNITIVE DECLINE AND SEX SPECIFICITY

Chronic anticholinergic use was specifically associated with a significant decline in visual memory or executive function in men and in verbal retrieval in women (see Table 3 for *P* values). Our data indicate a specific effect on early retrieval but not on late retrieval, which could suggest an effect on the speed of information processing rather than on search processes.[32] For women, an effect on a global cognitive measure targeting more severe decline was also observed. Some of these alterations in cognitive performances have already been observed in previous cross-sectional studies[3-8] as well as in retrospective[9] and prospective[10,11] longitudinal studies, although possible sex differences were not previously considered.

In women, we observed an age-by-anticholinergic intake interaction effect, the oldest women being at higher risk of global cognitive decline (*P*=.002). Elderly persons are known to be more sensitive than the young to the cognitive toxic effects associated with acute anticholinergic drug administration, which has been ascribed to decreased central cholinergic function.[33-36] Our data suggest a significant (*P*=.002) age-related vulnerability to anticholinergics in elderly women, whereas no notable interaction was found in men, but the results could have been limited owing to the lower number of men in our sample.

Table 3. Cognitive Decline According to Pattern of Anticholinergic Drug Use (Continuing or Discontinuing) During the Follow-up Period[a]

	Model 0		Model 2	
Group	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Women (n=3819)[b]				
ΔIST total ≤ –6				
Discontinuing	1.49 (1.00-2.22)	.05	1.45 (0.98-2.17)	.07
Continuing	1.53 (1.13-2.06)	.006	1.46 (1.08-1.98)	.02
ΔBVRT ≤ –2				
Discontinuing	0.90 (0.60-1.35)	.61	0.84 (0.55-1.27)	.40
Continuing	1.27 (0.95-1.71)	.11	1.20 (0.89-1.62)	.24
ΔTMT A ≥ 16				
Discontinuing	0.81 (0.47-1.41)	.46	NA	NA
Continuing	1.14 (0.79-1.64)	.48	NA	NA
ΔTMT B ≥ 35				
Discontinuing	1.06 (0.65-1.73)	.81	NA	NA
Continuing	0.92 (0.64-1.34)	.68	NA	NA
ΔMMSE ≤ –2				
Discontinuing	1.07 (0.71-1.62)	.74	1.03 (0.68-1.56)	.88
Continuing	1.48 (1.10-1.97)	.009	1.42 (1.06-1.90)	.02
Men (n=2644)[b]				
ΔIST total ≤ –6				
Discontinuing	0.63 (0.30-1.34)	.23	NA	NA
Continuing	1.48 (0.87-2.51)	.14	NA	NA
ΔBVRT ≤ –2				
Discontinuing	1.18 (0.59-2.37)	.63	1.17 (0.58-2.37)	.65
Continuing	2.07 (1.24-3.45)	.005	1.94 (1.15-3.27)	.01
ΔTMT A ≥16				
Discontinuing	0.49 (0.17-1.44)	.20	NA	NA
Continuing	1.12 (0.58-2.17)	.74	NA	NA
ΔTMT B ≥ 35				
Discontinuing	0.97 (0.39-2.44)	.95	0.90 (0.36-2.26)	.82
Continuing	2.23 (1.23-4.03)	.008	1.94 (1.06-3.58)	.03
ΔMMSE ≤ –2				
Discontinuing	1.34 (0.67-2.66)	.41	NA	NA
Continuing	1.41 (0.84-2.36)	.19	NA	NA

Abbreviations: BVRT, Benton Visual Retention Test; CI, confidence interval; IST, Isaac Set Test; MMSE, Mini-Mental State Examination; NA, not applicable; OR, odds ratio; TMT, Trail Making Test.

[a] The 449 participants having taken anticholinergics intermittently during the follow-up were not considered in this analysis. Model 0 was adjusted for age; education; center; and baseline cognitive performance; and model 2 was adjusted for center; age; education; baseline cognitive performance; BMI; alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; *APOE*E4* (allele producing the ε4 type of apolipoprotein E); diabetes mellitus; asthma; depression; ischemic diseases; Parkinson disease; and hypertension (for men and women) as well as hormone therapy for women.

[b] Except for TMT, which concerned 3175 women and 2159 men.

Endocrinological factors can modulate cognitive function in elderly women.[37] Dumas et al[15,16] reported that short-term estrogen pretreatment could attenuate anticholinergic-induced cognitive impairments in 2 small RCTs with 15 and 22 postmenopausal women. In the present study we found an interactive effect on cognitive decline in early retrieval between anticholinergic intake and HT use, which suggests that estrogen status in postmenopausal women may be important for cholinergic system integrity.

We also observed a significant interaction between anticholinergic intake and apolipoprotein E; women who were taking anticholinergics and were *APOE*E4* positive were at a 2-fold higher risk of global cognitive decline ($P = .005$) than noncarriers ($P = .65$). In 2 RCTs[12,13] in which 24 cognitively intact elderly participants were administered a single dose of the muscarinic antagonist trihexyphenidyl, the participants who were *APOE*E4* positive but not those who were *APOE*E4* negative demonstrated notable impairment in total and delayed recall 5 hours after treatment. Sex differences were not considered in these small RCTs, although a greater deleterious effect of *APOE*E4* on gross hippocampal pathologic characteristics and memory performance has been reported in women than in men with MCI.[38] Our data suggest that the *APOE*E4* could play an important role in increasing long-term cognitive vulnerability to chronic anticholinergic burden in the elderly population and that this effect could be particularly evident in postmenopausal women. Estrogen has been reported to be associated with less cognitive decline among *APOE*E4*-negative women but not *APOE*E4*-positive women.[39] Both characteristics (*APOE*E4*-negative women taking HT) may thus contribute to a higher protective effect against anticholinergic neurotoxic effects.

DEMENTIA

We observed an important association between anticholinergic use at baseline and the risk of developing dementia at 4-year follow-up. In a previous study[10] con-

ducted with an independent cohort, we found anticholinergic use to be a risk factor for MCI, but the numbers of patients with dementia were insufficient to determine the risk of dementia incidence. In the present study, we observed that chronic anticholinergic users were at higher risk of incident dementia compared with nonusers or persons having discontinued intake at the beginning of the follow-up. Although this finding has not been previously reported to our knowledge, it agrees with the study by Perry et al[40] on autopsied patients with Parkinson disease treated with anticholinergics; Alzheimer-type disease was observed in patients who had been treated for more than 2 years compared with those treated with short-term anticholinergics or untreated patients.

Several mechanisms may be postulated to explain how anticholinergic drug use may increase dementia risk. One possibility is neurotransmitter downregulation.[41] There is also the possibility of misdiagnosis of early dementia when in fact the patients are experiencing cognitive decline secondary to anticholinergic drug use.

STUDY LIMITATIONS

The data concerning some of the covariates were self-reported, with eventual subsequent recall bias. Bias could also have been introduced through the exclusion of participants, those lost to follow-up being more likely to have dementia and to be female, older, and with lower education level and baseline cognitive scores and more frequent use of anticholinergics. The higher dropout rate in this group may also limit the generalizability of our results. Furthermore, there are several methods for estimating anticholinergic burden. All of them have merits and limitations, with no ideal evidence-based approach.[42] We did not use in vitro or ex vivo measurement of anticholinergic activity (using radio-labeled muscarinic agonist) but rather a method based on anticholinergic drug lists, which is the only clinically useful method for routine clinical practice. We did not consider treatment compliance, which may have caused classification bias. Because we did not have data on precise duration of medication use, we could not definitively address the question of whether the effects are essentially transient or whether prolonged use could precipitate nonreversible dementia. Besides, we cannot exclude the possibility that there are other unknown factors, including subclinical disease (in addition to that detectable through the analysis of lipids, glycemia, and hypertension), which may confound the association between anticholinergic report and cognitive decline or dementia. Finally, because multiple analyses have been performed, we cannot exclude the possibility that some observed associations were the result of a chance finding.

STUDY STRENGTHS

The data used in the analysis come from a large, multicenter, population-based prospective study of people 65 years or older. Anticholinergic use was verified by examining the prescriptions and medications themselves, thus minimizing exposure misclassification. We have already reported within the same cohort that interviews and reimbursement data could estimate current exposure to chronically used drugs (including anticholinergic medication) similarly, with the advantage of self-medication being better described with interviews.[43] Finally, we have taken into account a wide range of competing causes of cognitive dysfunction in elderly individuals by controlling for sociodemographic, genetic, health, and lifestyle covariates and thus limiting any potential confounding. Despite this, there were only minor changes between the unadjusted and adjusted analysis, notably after adjusting for diseases associated with anticholinergic indication, suggesting independence of associations.

Table 4. Patterns of Anticholinergic Use (Continuing or Discontinuing) During Follow-up and Incident Dementia (Cox Model With Delayed Entry)[a]

Group	HR (95% CI)	*P* Value
All participants with dementia (n=177)	n=6463	
Discontinuing	1.28 (0.59-2.76)	.53
Continuing	1.65 (1.00-2.73)	.05
Participants with Alzheimer dementia (n=113)	n=6399	
Discontinuing	1.72 (0.74-3.99)	.21
Continuing	1.94 (1.01-3.72)	.05

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The participants who used anticholinergics intermittently during follow-up were not considered in this analysis. The model was adjusted for center; age; sex; education; body mass index; alcohol, tobacco, and caffeine intake; mobility; hypercholesterolemia; *APOE*E4* (allele producing the ε4 type of apolipoprotein E); diabetes mellitus; asthma; depression; ischemic diseases; Parkinson disease; and hypertension.

In conclusion, findings from this study suggest that the use of medication with anticholinergic effects was associated with an increased risk of cognitive dysfunction and dementia in elderly persons. Discontinuing anticholinergic treatment was associated with a decreased risk. Physicians should monitor current anticholinergic drug use in elderly patients and seek pharmacological alternatives before considering administration of neuroprotective medications to persons with MCI, thus escalating a prescription cascade involving cholinesterase inhibitors and anticholinergic drugs.[10,44,45] This is especially important considering that long-term concomitant therapy with anticholinergics may be associated with clinically significant deleterious effects on acetylcholinesterase therapy and may have adverse effects on the clinical course of Alzheimer disease.[46,47]

Accepted for Publication: April 30, 2009.
Correspondence: Marie-Laure Ancelin, PhD, Inserm, U888, Hôpital La Colombiere, pav 42, 39, avenue C. Flahault, BP 34493, 34093 Montpellier CEDEX 5, France (marie-laure.ancelin@inserm.fr).
Author Contributions: *Study concept and design:* Dartigues, Ritchie, and Ancelin. *Acquisition of data:* Dartigues and Rouaud. *Analysis and interpretation of data:* Carrière, Fourrier-Reglat, Pasquier, and Ancelin. *Drafting of the manuscript:* Carrière, Fourrier-Reglat, and Ancelin. *Critical revision of the manuscript for important intellectual content:* Dartigues, Rouaud, Pasquier, and Ritchie. *Statistical analysis:* Carrière, Fourrier-Reglat, and Ancelin. *Obtained funding:* Dartigues and Ritchie. *Study supervision:* Ancelin.

Financial Disclosure: None reported.
Funding/ Support: The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The 3C-Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education Nationale, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon, Fondation de France, and the Ministry of Research-Inserm Programme "Cohorts and collection of biological material." The Lille Génopôle received an unconditional grant from Eisai. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study.
Additional Information: An eTable is available at http://www.archinternmed.com.
Additional Contributions: The Génopôle of Lille, the Laboratories of Biochemistry of the University Hospitals of Dijon and Montpellier, the Town Council of Dijon, and the Conseil Général of Côte d'Or contributed to this study.

REFERENCES

1. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging*. 1999;15(1):15-28.
2. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundam Clin Pharmacol*. 2007;21(3):217-230.
3. Mulsant BH, Pollock BG, Kirshner M, Shen C, Dodge H, Ganguli M. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch Gen Psychiatry*. 2003;60(2):198-203.
4. Lechevallier-Michel N, Molimard M, Dartigues JF, Fabrigoule C, Fourrier-Reglat A. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol*. 2005;59(2):143-151.
5. Cao YJ, Mager DE, Simonsick EM, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. *Clin Pharmacol Ther*. 2008;83(3):422-429.
6. Cancelli I, Gigli GL, Piani A, et al. Drugs with anticholinergic properties as a risk factor for cognitive impairment in elderly people: a population-based study. *J Clin Psychopharmacol*. 2008;28(6):654-659.
7. Nebes RD, Pollock BG, Meltzer CC, et al. Serum anticholinergic activity, white matter hyperintensities, and cognitive performance. *Neurology*. 2005;65(9):1487-1489.
8. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. *Arch Intern Med*. 2007;167(8):781-787.
9. Bottiggi KA, Salazar JC, Yu L, et al. Long-term cognitive impact of anticholinergic medications in older adults. *Am J Geriatr Psychiatry*. 2006;14(11):980-984.
10. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006;332(7539):455-459.
11. Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *J Am Geriatr Soc*. 2008;56(12):2203-2210.
12. Pomara N, Belzer K, Hernando R, De La Pena C, Sidtis JJ. Increased mental slowing associated with the APOE epsilon4 allele after trihexyphenidyl oral anticholinergic challenge in healthy elderly. *Am J Geriatr Psychiatry*. 2008;16(2):116-124.
13. Pomara N, Willoughby LM, Wesnes K, Sidtis JJ. Increased anticholinergic challenge-induced memory impairment associated with the APOE-epsilon4 allele in the elderly: a controlled pilot study. *Neuropsychopharmacology*. 2004;29(2):403-409.
14. Artero S, Ancelin ML, Portet F, et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry*. 2008;79(9):979-984.
15. Dumas J, Hancur-Bucci C, Naylor M, Sites C, Newhouse P. Estrogen treatment effects on anticholinergic-induced cognitive dysfunction in normal postmenopausal women. *Neuropsychopharmacology*. 2006;31(9):2065-2078.
16. Dumas J, Hancur-Bucci C, Naylor M, Sites C, Newhouse P. Estradiol interacts with the cholinergic system to affect verbal memory in postmenopausal women: evidence for the critical period hypothesis. *Horm Behav*. 2008;53(1):159-169.
17. 3C Study Group. Vascular factors and risk of dementia: Design of the three city study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22(6):316-325.
18. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. *Br J Psychiatry*. 1973;123(575):467-470.
19. Benton A. *Manuel pour l'Application du Test de Rétention Visuelle: Applications Cliniques et Expérimentales*. Paris, France: Centre de Psychologie Appliquée; 1965.
20. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
22. Ritchie K, Carriere I, de Mendonca A, et al. The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology*. 2007;69(6):536-545.
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
24. World Health Organization. *World Health Organization Collaborating Centre for Drug Statistics Methodology: Guidelines for ATC Classification and DDD Assignment*. Oslo, Norway: WHO; 2000.
25. Thériaque Web site. http://www.theriaque.org. Accessed January 15, 2009.
26. Banque de Données Automatisée sur les Médicaments (BIAM) Web site. http://www2.biam2.org. Accessed January 15, 2009.
27. VIDAL Web site. http://www.vidal.fr. Accessed January 15, 2009.
28. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385-401.
29. Commenges D, Letenneur L, Joly P, Alioum A, Dartigues JF. Modelling age-specific risk: application to dementia. *Stat Med*. 1998;17(17):1973-1988.
30. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. *J Neurol Neurosurg Psychiatry*. 2002;73(4):390-394.
31. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology*. 2001;56(1):37-42.
32. Fernaeus SE, Almkvist O. Word production: dissociation of two retrieval modes of semantic memory across time. *J Clin Exp Neuropsychol*. 1998;20(2):137-143.
33. Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. *Psychopharmacology (Berl)*. 1992;107(2-3):437-441.
34. Molchan SE, Martinez RA, Hill JL, et al. Increased cognitive sensitivity to scopolamine with age and a perspective on the scopolamine model. *Brain Res Brain Res Rev*. 1992;17(3):215-226.
35. Ray PG, Meador KJ, Loring DW, Zamrini EW, Yang XH, Buccafusco JJ. Central anticholinergic hypersensitivity in aging. *J Geriatr Psychiatry Neurol*. 1992;5(2):72-77.
36. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5(3):263-303.
37. Ancelin ML, Ritchie K. Lifelong endocrine fluctuations and related cognitive disorders. *Curr Pharm Des*. 2005;11(32):4229-4252.
38. Fleisher A, Grundman M, Jack CR Jr, et al; Alzheimer's Disease Cooperative Study. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Arch Neurol*. 2005;62(6):953-957.
39. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology*. 2000;54(10):1949-1954.
40. Perry EK, Kilford L, Lees AJ, Burn DJ, Perry RH. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol*. 2003;54(2):235-238.
41. Fisher A, Pittel Z, Haring R, et al. M1 muscarinic agonists can modulate some of the hallmarks in Alzheimer's disease: implications in future therapy. *J Mol Neurosci*. 2003;20(3):349-356.
42. Rudd KM, Raehl CL, Bond CA, Abbruscato TJ, Stenhouse AC. Methods for assessing drug-related anticholinergic activity. *Pharmacotherapy*. 2005;25(11):1592-1601.
43. Noize P, Bazin F, Dufouil C, et al. Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) Study. *Pharmacoepidemiol Drug Saf*. 2009;18(4):310-319.
44. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315(7115):1096-1099.
45. Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med*. 2005;165(7):808-813.
46. Lu CJ, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am J Geriatr Psychiatry*. 2003;11(4):458-461.
47. Cancelli I, Valentinis L, Merlino G, Valente M, Gigli GL. Drugs with anticholinergic properties as a risk factor for psychosis in patients affected by Alzheimer's disease. *Clin Pharmacol Ther*. 2008;84(1):63-68.