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Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population.

The Three-City Study

Running title: Anticholinergics and cognitive dysfunction

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ABSTRACT

Objective: To examine the association between use of medications with anticholinergic properties, cognitive decline and incident dementia in a large community-based sample of subjects aged 65 years and over.

Methods: Participants were 4128 women and 2784 men from a population-based cohort recruited from three French cities. Cognitive performance, clinical diagnosis of dementia and anticholinergic use were evaluated at base-line, 2 and 4 year later.

Results: 7.5% of subjects reported anticholinergic drug use at base-line. Multivariate adjusted logistic regression indicated that women reporting anticholinergic drugs at base-line showed greater decline over four years in verbal fluency scores (OR=1.41, CI=1.11-1.79) and in global cognitive functioning (OR=1.22, 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, CI=1.08-2.47) and to a lesser extent in executive function (OR=1.47, CI=0.89-2.44). Significant interactions were observed in women between anticholinergic use and age, apolipoprotein E, or hormone replacement therapy. A significantly 1.4-2 fold higher risk of cognitive decline was observed for continuous anticholinergic users but not for those having discontinued. The risk of incident dementia over the four-year follow-up was also increased in continuous users (HR=1.65, CI=1.00-2.73) but not in those having discontinued anticholinergic drugs (HR=1.28, 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 oldest old and persons at high genetic risk of cognitive disorder.

INTRODUCTION

In the absence of an effective clinical treatment for age-related neuro-degenerative 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 or short-term administration of anticholinergic medication and delirium.¹ Few community studies have however, been undertaken in spite of the relatively high intake of over-the-counter and prescription drugs consumed by the elderly.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 sub-clinical cognitive decline thus remains unclear due to the scarcity of longitudinal population studies. In a retrospective study of 592 older adults, Bottiggi et al. observed an accelerated decline over a six-year period of psychomotor speed and executive functioning in anticholinergic users.⁹ In a sample of 372 elderly subjects, we have previously reported a significant association between continuous anticholinergic use over one year and poorer performance on specific cognitive domains.¹⁰ Most importantly, anticholinergic drug use was observed to be a strong predictor of mild cognitive impairment (MCI) although risk of subsequent dementia could not be estimated due to small numbers. 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, previous studies have not examined genetic vulnerability although two small randomized controlled trials (RCTs) suggested increased cognitive sensitivity in subjects with an apolipoprotein E (ApoE) $\epsilon 4$ allele shortly after acute anticholinergic administration.^{12, 13} Gender 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 replacement therapy (HRT). This hypothesis has yet to be tested.

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

SUBJECTS AND METHODS

Study population

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities between 1999 and 2001.¹⁷ The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. The subjects were followed up every 2 years for 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 one base-line adjustment variable. The present analyses were conducted on 6912 subjects. Of these, 914 subjects (13.2%) had only one follow-up examination. The average follow-up (SD) was 3.5 years (0.6). Subjects not included in the present analysis were more frequently women, older, with lower education level, more frequently using anticholinergics, and with lower base-line cognitive scores (data not shown). There were 59.7% of women in the sample. The mean age (SD) was 73.6 (5.3) for men and 73.8 (5.2) for women.

Cognitive outcome measures

A battery of cognitive tests assessed different areas of cognitive functioning. Isaacs Set Test¹⁸ provided a measure of verbal fluency or semantic access which 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”). Benton’s Visual Retention Test (BVRT)¹⁹ assessed visual memory; psychomotor speed and executive function were assessed with the Trail Making Tests A and B respectively (TMA and TMB)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 base-line, and during wave 1 and 2 of the follow-up, except the TMT A and B, which were not given in wave 1. 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 base-line 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 3C study local clinical investigators according to DSM-IV 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 (ATC) Classification.²⁴ The list of drugs with anticholinergic properties was established from Theriaque (<http://www.theriaque.org>), BIAM (<http://www2.biam2.org>) and VIDAL classifications (<http://www.vidal.fr>).

Socio-demographic 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 HRT for women. History of stroke, angina pectoris, myocardial infarction and cardio-vascular surgery was established according to standardized questions with additional information where necessary from general practitioners. Recent asthma crisis, hypertension, hypercholesterolemia and diabetes were also recorded. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression Scale (CES-D)²⁵ with a 16 cut-off point. Fasting blood samples were taken for cholesterol levels and ApoE genotyping as described previously.²²

Statistical analyses

We used univariate and multivariate logistic regression analyses to determine if base-line consumption of anticholinergic drugs was associated with odds of cognitive decline. Men and women were examined in separate analyses as they differed in both anticholinergic drug use and profiles of cognitive ability. The Chi2 test was used to identify gender-related differences. After gender stratification, univariate odds ratios were adjusted for centre, age, educational level, and base-line cognitive performance (**model 0**). Multivariate adjusted logistic regression included covariates that were associated with cognitive decline ($p < 0.15$). **Model 1** was adjusted for centre, age, education, base-line cognitive performance, body mass index (BMI), alcohol, tobacco, and caffeine intake,

mobility, hypercholesterolemia, ApoE, diabetes, asthma, and HRT for women. Compared to model 1, **model 2** was further adjusted for pathologies associated with anticholinergic drug use in order to take into account a possible prescription bias, *e.g.* depression, ischemic pathologies, Parkinson's disease, and hypertension. For analyses taking into account number of anticholinergic medications we used model 2 where gender was an adjustment variable (instead of stratifying by sex) due to low numbers in several categories.

A Cox model with delayed entry was used in the analysis of dementia incidence taking age as the basic time scale and birth as the time origin.²⁶ This analysis was undertaken on 7123 subjects without missing data for base-line adjustment variables but with possibly missing repeated cognitive testing. The analyses were not stratified by sex to allow full adjustment in spite of relatively small numbers of incident cases. The full model was adjusted for sex, centre, education, BMI, alcohol, tobacco and caffeine intake, mobility, hypercholesterolemia, ApoE, diabetes, asthma, depression, ischemic pathologies, Parkinson's disease and hypertension. Analyses were carried out using SAS software (version 9.1).

RESULTS

Population characteristics

Within this elderly community-dwelling population, 520 of the 6912 subjects (7.5%) were taking anticholinergic drugs at base-line, of whom 36 subjects (6.9%) were taking two anticholinergic drugs simultaneously, and eight (1.5%) three. The main drug classes consisted of antidepressants (1.9%), digestive antispasmodics (1.6%), genital-urinary antispasmodics (1.3%), H1-anti-histaminics (1.0%), anxiolytics (0.9%), cardiovascular medications (0.5%), antiepileptics (0.5%), antipsychotics (0.3%), antiasthmatics (0.1%), and antiparkinson drugs (0.1%) (see Appendix for detail). None of the subjects reported use of cholinesterase inhibitors.

Overall women reported more often anticholinergic drug use than men (9.6% vs. 4.4%, respectively, $p < 0.0001$). Men and women were found to differ on all other characteristics at base-line

except Apoε4. They also differed in base-line cognitive performance with a higher proportion of women showing low scores on the MMSE, Benton test, and TMT A and 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 subjects with depression ($p<0.001$), in low alcohol consumers ($p=0.02$ in women and $p=0.0009$ in men) and with poor mobility ($p=0.03$ in women and $p<0.0001$ in men) (**Table 1**). Women not consuming caffeine ($p=0.008$), or with diabetes ($p=0.007$), ischemic pathologies ($p=0.02$) or Parkinson's disease ($p=0.0001$) were more frequent anticholinergic drug users.

Associations between anticholinergics and cognitive decline over 4-year follow-up

In the longitudinal logistic regression analyses, decline in cognitive performance was defined as a decrease from base-line of at least 6 points on the Isaacs total score or at least two points on the Benton test and the MMSE (lowest quintiles). For TMT, cognitive decline was defined as an increase from base-line of at least 16 (TMTA) or 35 seconds (TMTB) (**Table 2**). In women, univariate logistic regression adjusted on age, educational level, centre, and base-line cognitive score (**model 0**) indicated a significant association between anticholinergic use and decline in Isaacs total score ($OR=1.47$, $CI=1.16-1.86$, $p=0.002$) and in the MMSE ($OR=1.26$, $CI=1.00-1.60$, $p=0.05$). No significant association was observed for the Benton test and the TMT A or B. In men, anticholinergic report was significantly associated with decline in the Benton test ($OR=1.70$, $CI=1.13-2.56$, $p=0.01$) and nearly significantly in the TMTB ($OR=1.61$, $CI=0.98-2.64$, $p=0.06$) but not in the Isaacs test or the TMTA. In multivariate logistic regression (**model 1**) the same associations were observed with significant cognitive decline in the Isaacs test in women and in the Benton test in men. These associations persisted in the complete model (**model 2**) further adjusted for other confounders such as pathologies associated with anticholinergic prescription (depression, ischemic pathologies, Parkinson's disease, and hypertension). The odds ratio was 1.41 ($CI=1.11-1.79$, $p=0.006$) for decline on the Isaacs total score in women. This effect appeared related to the early retrieval phase

(OR=1.27, CI=0.99-1.62, $p=0.06$) whereas no significant association was found for the late retrieval (data not shown). In men, the OR was 1.63 (CI=1.08-2.47, $p=0.02$) for decline in the Benton test. On the other hand, the association with decline in the TMTB in men was no more significant in model 2 ($p=0.14$), as well as for MMSE in women ($p=0.10$). For women specifically, an interaction was observed on the MMSE between anticholinergic use and age (risk increasing with age, $p=0.002$) and ApoE (the risk being significantly increased only for allele $\epsilon 4$ carriers, OR=2.05 CI=1.24-3.40, $p=0.005$ vs. OR=1.07 CI=0.81-1.40, $p=0.65$ in non $\epsilon 4$ carriers). There was also an interaction between anticholinergic use and HRT on early retrieval on the Isaacs; the risk of cognitive decline using anticholinergics being increased for never HRT users (OR=1.44 CI=1.07-1.94, $p=0.02$) in contrast with current HRT users (OR=0.51 CI=0.25-1.05, $p=0.07$).

Cognitive decline according to the pattern of the anticholinergic drug use during follow-up

A total of 5969 (86.4%) subjects did not report anticholinergic drug use at base-line nor at the later follow-up examinations, 175 (2.5%) reported anticholinergic use only at base-line, but not at either 2- or 4-year follow-up (“discontinuing” group), and 319 (4.6%) reported anticholinergic drug use both at base-line and at least at the 2-year examination (“continuing” group), of whom 204 were also users at the 4-year follow-up. Other subjects having reported anticholinergics intermittently during the follow-up ($n=449$) were not considered in the following analyses.

Compared to women who had never reported anticholinergic drugs, women of the “continuous” group were at higher risk of cognitive decline on the Isaacs test in fully-adjusted models (OR=1.46, CI=1.08-1.98, $p=0.02$), and on the MMSE (OR=1.42, CI=1.06-1.90, $p=0.02$) (**Table 3**). The same pattern was observed for men in the “continuous” group in relation to decline in the Benton test (OR=1.94, CI=1.15-3.27, $p=0.01$) and the TMTB (OR=1.94, CI=1.06-3.58, $p=0.03$). On the other hand, the risk was not significantly modified for subjects having discontinued anticholinergic drugs.

Associations between base-line anticholinergic drug use and 4-year incidence of dementia

Of the 7123 subjects included in the analysis concerning dementia outcome, there were 221 newly diagnosed cases during follow-up, of whom 143 had Alzheimer's disease. In the sub-sample from which intermittent users were excluded, a multi-adjusted delayed-entry Cox model shows an increased risk for incident dementia or Alzheimer's disease for persons having used anticholinergic drugs continuously (HR=1.65, CI=1.00-2.73, p=0.05 and HR=1.94, CI=1.01-3.72, p=0.05, respectively) but not for those having discontinued anticholinergic treatment after the inclusion (Table 4).

DISCUSSION

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 co-determinants of cognitive decline. It should be mentioned that similar results were obtained in the unadjusted model (model 1) and in the model that adjusted for the pathologies 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 appeared reversible after anticholinergic treatment was discontinued. This could at least partly account for the reversible dementia observed in some patients with MCI.^{27, 28}

Association between anticholinergics and cognitive decline and gender 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. Our data indicate a specific effect on early retrieval but not late retrieval which could suggest an effect on speed of information processing rather than on search processes.²⁹ 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 studies³⁻⁸ as well as in retrospective,⁹ and prospective^{10, 11} longitudinal studies although possible gender 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 ($p=0.002$). The elderly are known to be more sensitive than the young to cognitive toxicity associated with acute anticholinergic drug administration, which has been ascribed to decreased central cholinergic function.³⁰⁻³³ Our data suggest a significant age-related vulnerability to anticholinergics in elderly women whereas no significant interaction was found in men, but the results could have been limited due to the lower number of men in our sample.

Endocrinological factors can modulate cognitive function in elderly women.³⁴ Dumas et al. reported that short-term estrogen pretreatment could attenuate anticholinergic-induced cognitive impairments in two small RCTs with 15 and 22 postmenopausal women.^{15, 16} In the present study we found an interactive effect on cognitive decline in early retrieval between anticholinergic intake and HRT 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 ApoE; women taking anticholinergics and carrying $\epsilon 4$ allele being at 2-fold higher risk of global cognitive decline than non-carriers. In two RCTs in which 24 cognitively intact elderly subjects were administered a single dose of the muscarinic antagonist, trihexyphenidyl, the $\epsilon 4$ allele positive but not the $\epsilon 4$ negative participants demonstrated significant impairment in total and delayed recall 5h after treatment.^{12, 13} Gender differences were not considered in these small RCTs although a greater deleterious effect of ApoE4 on gross hippocampal pathology and memory performance has been reported in women than in men with MCI.³⁵ Our data suggest that the $\epsilon 4$ allele could play a significant role in increasing long-term cognitive vulnerability to chronic anticholinergic burden in 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 $\epsilon 4$ -negative women but not $\epsilon 4$ -positive women.³⁶ Both characteristics ($\epsilon 4$ -negative women taking HRT) may thus contribute to a higher protective effect against anticholinergic neurotoxicity.

Dementia

We observed a significant association between anticholinergic use at base-line and the risk of developing dementia at 4-year follow-up. In a previous study conducted on an independent cohort we found anticholinergic report to be a risk factor for MCI, but numbers were insufficient to determine risk of dementia incidence.¹⁰ In the present study, we observed that chronic anticholinergic users were at higher risk of incident dementia compared to non users, or persons having discontinued intake at the beginning of the follow-up. While this finding has not been previously reported, this agrees with the study by Perry et al. on autopsied Parkinson's disease patients treated with anticholinergics; Alzheimer-type pathology being observed in patients who had been treated for more than two years compared to short-term anticholinergic treated or untreated cases.³⁷

Several mechanisms may be postulated to explain how anticholinergic drug use may increase dementia risk. One possibility is neurotransmitter down-regulation.³⁸ There is also the possibility of misdiagnosis of early dementia when in fact the patients are suffering from cognitive decline secondary to anticholinergic drug use.

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, women, older, with lower education level and base-line cognitive scores and more frequent anticholinergic users. 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 approach³⁹. We did not use *in vitro* or *ex vivo* measurement of anticholinergic activity (using radiolabeled muscarinic agonist) but 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. Since 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 non-reversible dementia. Besides, we cannot exclude 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, since multiple analyses have been performed we cannot exclude that some observed associations were due to a chance finding.

Strengths

The data used in the analysis comes from a large multicentre population-based prospective study of people aged 65 years and over. 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 that self-medication being better described with interviews.⁴⁰ Finally, we have taken into account a wide range of competing causes of cognitive dysfunction in the elderly, by controlling for socio-demographic, 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 pathologies associated with anticholinergic indication suggesting independence of associations.

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. Medical practitioners 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, 41, 42} This is especially important considering that long-term concomitant therapy with anticholinergics may be associated with significant deleterious effects on acetylcholinesterase therapy, and may have adverse effects on the clinical course of Alzheimer's disease.^{43, 44}

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REFERENCES

1. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging* 1999;15:15-28.
2. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundam Clin Pharmacol.* 2007;21:217-30.
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;60:198-203.
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;59:143-51.
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;83:422-9.
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;28:654-9.
7. Nebes RD, Pollock BG, Meltzer CC et al. Serum anticholinergic activity, white matter hyperintensities, and cognitive performance. *Neurology.* 2005;65:1487-9.
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;167:781-7.
9. Bottiggi KA, Salazar JC, Yu L et al. Long-term cognitive impact of anticholinergic medications in older adults. *Am J Geriatr Psychiatry.* 2006;14:980-4.
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;332:455-9.

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;56:2203-10.
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;16:116-24.
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;29:403-9.
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;79:979-984.
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;31:2065-78.
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;53:159-69.
17. The 3C Study Group. Vascular factors and risk of dementia: Design of the three city study and baseline characteristics of the study population. *Neuroepidemiology* 2003;22:316-325.
18. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. *Br J Psychiatry* 1973;123:467-70.
19. Benton A. Manuel pour l'application du test de rétention visuelle. Applications cliniques et expérimentales. Paris: Centre de Psychologie Appliquée; 1965.
20. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1965;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;12:189-98.

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;69:536-45.
23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th edn vol. Washington, DC: American Psychiatric Association; 1994.
24. WHO. World Health Organising Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo, Norway; 2000.
25. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement* 1977;1:385-401.
26. Commenges D, Letenneur L, Joly P, Alioum A, Dartigues JF. Modelling age-specific risk: application to dementia. *Stat Med* 1998;17:1973-88.
27. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. *J Neurol Neurosurg Psychiatry*. 2002;73:390-4.
28. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology* 2001;56:37-42.
29. Fernaeus SE, Almkvist O. Word production: dissociation of two retrieval modes of semantic memory across time. *J Clin Exp Neuropsychol*. 1998;20:137-43.
30. Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. *Psychopharmacology (Berl)* 1992;107:437-41.
31. 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;17:215-26.
32. Ray PG, Meador KJ, Loring DW, Zamrini EW, Yang XH, Buccafusco JJ. Central anticholinergic hypersensitivity in aging. *J Geriatr Psychiatry Neurol*. 1992;5:72-7.
33. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5:263-303.
34. Ancelin ML, Ritchie K. Lifelong endocrine fluctuations and related cognitive disorders. *Current Pharmaceutical Design* 2005;11:4229-52.

35. Fleisher A, Grundman M, Jack CR, Jr. et al. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Arch Neurol*. 2005;62:953-7.
36. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology* 2000;54:1949-1954.
37. Perry EK, Kilford L, Lees AJ, Burn DJ, Perry RH. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol*. 2003;54:235-8.
38. 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;20:349-56.
39. Rudd KM, Raehl CL, Bond CA, Abbruscato TJ, Stenhouse AC. Methods for assessing drug-related anticholinergic activity. *Pharmacotherapy*. 2005;25:1592-601.
40. 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. *Pharmacoepidemiology and Drug Safety* 2009;in press.
41. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315:1096-9.
42. Gill SS, Mamdani M, Naglie G et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med*. 2005;165:808-13.
43. Lu CJ, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am J Geriatr Psychiatry*. 2003;11:458-61.
44. 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;84:63-8.

Table 1. Characteristics of the study population as a function of anticholinergic use at baseline

Characteristic	Women			Men		
	ACH drugs		<i>P</i> Value	ACH drugs		<i>P</i> Value
	No	Yes		No	Yes	
	(n=3731) %	(n=397) %		(n=2661) %	(n=123) %	
Age						
65-69	25.5	23.2	.30	26.4	19.5	.25
70-74	33.1	30.5		35.0	34.1	
75-80	27.7	30.5		24.6	28.5	
80+	13.7	15.8		14.0	17.9	
Education						
5 years	24.6	27.7	.11	21.4	30.1	.004
9 years	40.2	41.3		30.0	33.3	
12 years	21.0	20.9		19.5	22.0	
12 +	14.2	10.1		29.1	14.6	
CESD ≥ 16	26.4	42.3	< .0001	13.0	27.6	< .0001
Ischemic pathologies*	11.5	15.4	.02	22.1	23.6	.70
BMI						
Normal	53.9	51.9	.73	38.1	35.8	.85
Overweight	32.8	34.5		49.2	50.4	
Obese	13.3	13.6		12.7	13.8	
Diabetes†	6.3	9.8	.007	12.7	17.1	.15
Asthma ‡	2.2	2.5	.65	1.3	2.4	.29
Hypertension§	53.5	50.9	.32	59.9	64.2	.34
Parkinson's disease	0.6	2.3	.0001	1.3	3.3	.07
Hypercholesterolemia	67.9	70.0	.39	83.5	82.9	.88
Alcohol						
0	26.4	32.8	.02	7.8	13.0	.0009
1-36 g/day	72.0	66.2		72.6	79.7	
> 36g/day	1.6	1.0		19.6	7.3	
Smoking						
Never	81.1	83.4	.51	30.2	26.8	.72
Former	15.2	13.1		61.7	64.2	
Current	3.7	3.5		8.1	9.0	
Caffeine consumption per day						
[0-1] unit	23.9	31.0	.008	27.4	26.8	.98
[1-3] units	59.4	54.2		59.3	60.2	
> 3 units	16.7	14.8		13.3	13.0	
Mobility						
Confined home	1.7	2.5	.03	1.0	3.3	< .0001
Confined neighborhood	4.1	6.6		1.8	6.5	
Not confined	94.2	90.9		97.2	90.2	
HRT						
Current	14.9	16.9	.57			
Former	16.8	16.1				
Never	68.3	67.0				
ApoE $\epsilon 4$	19.0	19.7	.77	20.7	17.1	.32

Table 1, cont.

MMSE < 26	15.2	17.9	.15	11.5	15.5	.18
Isaacs total score ¶ < 40	19.7	24.2	.03	20.1	22.8	.47
Benton test ¶ < 11	29.6	40.1	< .0001	22.8	40.7	< .0001
TMT A ¶ > 69°	18.0	25.8	.0007	13.9	21.7	.04
TMT B ¶ > 139°	18.7	27.0	.0003	15.9	25.0	.02

* History of stroke, myocardial infarction, angina pectoris, or arteritis.

† Diabetes defined as glucose ≥ 7 mmol/l or treated.

‡ Asthma crisis over the past year.

§ Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 mm Hg or intake of antihypertensive drugs.

|| Total cholesterol level ≥ 6.2 mmol/l or treated by lipid lowering agents.

¶ % of subjects with lowest cognitive performances at base-line (lowest quintile)

°The number of subjects who have the TMT tests were for women, 3125 non ACH users and 322 users and for men, 2177 non ACH users and 92 users (see Methods for detail).

Abbreviations: ACH = Anticholinergic BMI = body mass index; HRT = hormone replacement therapy

Table 2. Base-line anticholinergic use and cognitive decline over the 4-year follow-up period

	Model 0		Model 1		Model 2	
	OR [CI95]	p-value	OR [CI95]	p-value	OR [CI95]	p-value
WOMEN (n=4128*)						
Δ Isaacs total ≤ -6	1.47 [1.16-1.86]	0.002	1.44 [1.13-1.83]	0.003	1.41 [1.11-1.79]	0.006
Δ Benton ≤ -2	1.13 [0.89-1.43]	0.33				
Δ TMT A ≥ 16	1.05 [0.78-1.42]	0.73				
Δ TMT B ≥ 35	0.98 [0.73-1.31]	0.88				
Δ MMSE ≤ -2	1.26 [1.00-1.60]	0.05	1.25 [0.99-1.58]	0.07	1.22 [0.96-1.55]	0.10
MEN (n=2784*)						
Δ Isaacs30 ≤ -6	1.03 [0.67-1.59]	0.89				
Δ Benton ≤ -2	1.70 [1.13-2.56]	0.01	1.68 [1.11-2.53]	0.01	1.63 [1.08-2.47]	0.02
Δ TMT A ≥ 16	0.84 [0.48-1.46]	0.53				
Δ TMT B ≥ 35	1.61 [0.98-2.64]	0.06	1.58 [0.96-2.62]	0.07	1.47 [0.89-2.44]	0.14
Δ MMSE ≤ -2	1.39 [0.92-2.09]	0.12				

* Except for TMT which concerned 3447 women and 2269 men

Model 0: adjusted for centre, age, education, and baseline cognitive performance.

Model 1: adjusted for centre, age, education, base-line cognitive performance, BMI, alcohol, tobacco and caffeine intake, mobility, hypercholesterolemia, ApoE, diabetes, asthma, (for men and women) as well as HRT for women.

Model 2: adjusted for all the covariates in model 1, plus depression, ischemic pathologies, Parkinson's disease and hypertension (for men and women)

Table 3. Cognitive decline according to pattern of anticholinergic drug use during the follow-up period*

	MODEL 0		MODEL 2	
	OR (CI)	p	OR (CI)	p
WOMEN (n=3819†)				
ΔIsaacs total ≤ -6				
Discontinuing	1.49 [1.00-2.22]	0.05	1.45 [0.98-2.17]	0.07
Continuing	1.53 [1.13-2.06]	0.006	1.46 [1.08-1.98]	0.02
ΔBenton ≤ -2				
Discontinuing	0.90 [0.60-1.35]	0.61	0.84 [0.55-1.27]	0.40
Continuing	1.27 [0.95-1.71]	0.11	1.20 [0.89-1.62]	0.24
ΔTMT A ≥ 16				
Discontinuing	0.81 [0.47-1.41]	0.46		
Continuing	1.14 [0.79-1.64]	0.48		
ΔTMT B ≥ 35				
Discontinuing	1.06 [0.65-1.73]	0.81		
Continuing	0.92 [0.64-1.34]	0.68		
ΔMMSE ≤ -2				
Discontinuing	1.07 [0.71-1.62]	0.74	1.03 [0.68-1.56]	0.88
Continuing	1.48 [1.10-1.97]	0.009	1.42 [1.06-1.90]	0.02
MEN (n=2644†)				
ΔIsaacs total ≤ -6				
Discontinuing	0.63 [0.30-1.34]	0.23		
Continuing	1.48 [0.87-2.51]	0.14		
ΔBenton ≤ -2				
Discontinuing	1.18 [0.59-2.37]	0.63	1.17 [0.58-2.37]	0.65
Continuing	2.07 [1.24-3.45]	0.005	1.94 [1.15-3.27]	0.01
ΔTMT A ≥ 16				
Discontinuing	0.49 [0.17-1.44]	0.20		
Continuing	1.12 [0.58-2.17]	0.74		
ΔTMT B ≥ 35				
Discontinuing	0.97 [0.39-2.44]	0.95	0.90 [0.36-2.26]	0.82
Continuing	2.23 [1.23-4.03]	0.008	1.94 [1.06-3.58]	0.03
ΔMMSE ≤ -2				
Discontinuing	1.34 [0.67-2.66]	0.41		
Continuing	1.41 [0.84-2.36]	0.19		

* The 449 subjects having taken anticholinergics intermittently during the follow-up were not considered in this analysis.

† Except for TMT which concerned 3175 women and 2159 men.

Model 0: adjusted for age, education, centre, and base-line cognitive performance

Model 2: adjusted for centre, age, education, base-line cognitive performance, BMI, alcohol, tobacco and caffeine intake, mobility, hypercholesterolemia, ApoE, diabetes, asthma, depression, ischemic pathologies, Parkinson's disease and hypertension (for men and women) as well as HRT for women.

Table 4. Patterns of anticholinergic use during follow-up and incident dementia (Cox model with delayed entry)*

	HR [†] (CI)	p
All dementia (n=177)	n=6463	
Discontinuing	1.28 [0.59-2.76]	0.53
Continuing	1.65 [1.00-2.73]	0.05
Alzheimer's dementia (n=113)	n=6399	
Discontinuing	1.72 [0.74-3.99]	0.21
Continuing	1.94 [1.01-3.72]	0.05

[†] adjusted for centre, age, sex, education, BMI, alcohol, tobacco and caffeine intake, mobility, hypercholesterolemia, ApoE, diabetes, asthma, depression, ischemic pathologies, Parkinson's disease and hypertension.

Appendix. Frequency of use of drugs considered to possess anticholinergic activity*

CHEMICAL ACTIVE SUBSTANCE	Frequency (%)
ANTIDEPRESSANTS	
AMITRIPTYLINE	0.87
AMOXAPINE	0.03
CLOMIPRAMINE	0.54
DOSULEPINE	0.14
DOXEPINE	0.06
IMIPRAMINE	0.06
MAPROTILINE	0.10
MIRTAZAPINE	0.03
VILOXAZINE	0.03
OPIPRAMOL	0.01
TRIMIPRAMINE	0.04
DIGESTIVE ANTISPASMODICS	
ALVERINE	1.10
ATROPINE	0.03
TIEMONIUM	0.04
CLIDINIUM	0.39
GENITAL-URINARY ANTISPASMODICS	
FLAVOXATE	0.06
OXYBUTYNIN	1.20
TOLTERODINE	0.04
H1-ANTI-HISTAMINICS	
ALIMEMAZINE	0.10
DEXCHLORPHENIRAMINE	0.04
DOXYLAMINE	0.16
FLUNARIZINE	0.26
KETOTIFENE	0.04
MECLOZINE	0.04
MEQUITAZINE	0.04
MIZOLASTINE	0.10
OXATOMIDE	0.06
PHENYLPROPANOLAMINE	0.01
PIMETHIXENE	0.01
PIZOTIFEN	0.04
PROMETHAZINE	0.09
ANXIOLYTICS	
ACEPROMETAZINE	0.29
HYDROXYZINE	0.62
CARDIOVASCULAR MEDICATIONS	
DISOPYRAMIDE	0.45
ANTIEPILEPTICS	
CARBAMAZEPINE	0.46
ANTIPSYCHOTICS	
CHLORPROMAZINE	0.01
CYAMEMAZINE	0.06
FLUPENTIXOL	0.01
FLUPHENAZINE	0.01
LEVOMEPRIMAZINE	0.19
PERICIAZINE	0.03
THIORIDAZINE	0.01
TRIFLUOPERAZINE	0.01

Appendix, cont.

ANTIASTHMATIC	
IPRATROPIUM BROMIDE	0.15
ANTIPARKINSON DRUGS	
TROPATEPINE	0.03
TRIHENXYPHENIDYL	0.09
ANTIEMETICS	
METOPIMAZINE	0.07

*The list was established using BIAM, THERIAQUE and VIDAL classifications and drugs were coded according to the World Health Organization's ATC classification (see Methods). Some subjects used two or three medications with anticholinergic properties simultaneously.