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## Research

### **Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study**

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## Abstract

**Objective** To assess the potential of anticholinergic drugs as a cause of non-degenerative mild cognitive impairment in elderly people.

**Design** Longitudinal cohort study.

**Setting** 63 randomly selected general practices in the Montpellier region of southern France.

**Participants** 372 people aged >60 years without dementia at recruitment.

**Main outcome measures** Anticholinergic burden from drug use, cognitive examination, and neurological assessment.

**Results** 9.2% of subjects continuously used anticholinergic drugs during the year before cognitive assessment. Compared with non-users, they had poorer performance on reaction time, attention, delayed non-verbal memory, narrative recall, visuospatial construction, and language tasks but not on tasks of reasoning, immediate and delayed recall of wordlists, and implicit memory. Eighty per cent of the continuous users were classified as having mild cognitive impairment compared with 35% of non-users, and anticholinergic drug use was a strong predictor of mild cognitive impairment (odds ratio 5.12,  $P=0.001$ ). No difference was found between users and non-users in risk of developing dementia at follow-up after eight years.

**Conclusions** Elderly people taking anticholinergic drugs had significant deficits in cognitive functioning and were highly likely to be classified as mildly cognitively impaired, although not at increased risk for dementia. Doctors should assess current use of anticholinergic drugs

in elderly people with mild cognitive impairment before considering administration of acetylcholinesterase inhibitors.

## Introduction

Mild cognitive impairment is a general term used to describe subclinical cognitive deficits in elderly people that are likely to evolve towards dementia.[1] [2] Longitudinal, population based studies have shown that most people with mild cognitive impairment do not develop dementia even after five to 10 years of follow-up,[3-6] yet little is known about the causes of such non-degenerative cognitive impairment, as epidemiological studies have almost exclusively focused on risk factors for neurodegenerative disease.

Experimental and clinical studies have consistently shown that dysfunction of the cholinergic system has a detrimental impact on cognitive performance. Administration of an anticholinergic agent, scopolamine 0.4 mg, has been shown to reduce hippocampal activation on functional magnetic resonance imaging during a name-face recall task[7] and, when given to young adults, produces cognitive deficits characteristic of ageing related changes rather than dementia—that is, impaired attention and praxis, delayed memory, and reduced psychomotor speed with relative sparing of implicit memory and linguistic and reasoning abilities.[8-10]

Drug consumption in elderly people is high, and many commonly prescribed drugs have anticholinergic effects (such as antiemetics, antispasmodics, bronchodilators, antiarrhythmic drugs, antihistamines, analgesics, antihypertensives, antiparkinsonian agents, corticosteroids, skeletal muscle relaxants, ulcer drugs, and psychotropic drugs). Furthermore, such drugs are likely to have a more toxic effect in an ageing brain because of increased permeability of the blood brain barrier, slower metabolism and drug elimination, and polypharmacy. In US nursing homes more than 30% of elderly residents take more than two anticholinergic drugs, and 5% take more than five,[11] [12] and an estimated 51% of the general population use anticholinergic drugs.[13]

Not only do doctors commonly fail to associate cognitive dysfunction in elderly people with anticholinergic agents, they also underestimate anticholinergic toxicity,[12] prescribing such drugs at high to excessive doses.[14] Moreover, an increasing number of such compounds are available without prescription, so there is a high risk of unregulated toxicity.[15]

In order to test whether drug induced anticholinergic burden is associated with cognitive dysfunction similar to mild cognitive impairment, we used data from a longitudinal general population study that included a comprehensive cognitive examination.[16]

## Methods

### Subjects

The Eugeria longitudinal study of cognitive ageing recruited participants aged >60 years through 63 randomly selected general practitioners in the Montpellier region of southern France and is described in detail elsewhere.[16] Briefly, the study covered both urban and rural areas and included people in institutions. After a refusal rate of 7%, 372 elderly people without senile dementia (according to the criteria of *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)) at baseline were followed up annually for two years. Five per cent of participants refused one or more of the evaluations, principally because of ill health.

Participants were visited in their usual place of residence by a research interviewer with nursing training. A general health interview was conducted to obtain information on current and past illnesses and current depressive symptoms. A diagnosis of major depression was made by the application of DSM-III-R diagnostic criteria to symptom profiles. The interview included questions on drug use, and the interviewers asked to see currently used drugs and prescriptions where available. Habitual use of drugs obtained without prescription was also noted. Where necessary, confirmation was obtained from a proxy or the participant's general practitioner.

A consent form describing the aims and methods of the study was signed by all participants. Authorisation for the study was also obtained from the national data protection committee (CNIL) and the national ethics committee. The regional association of medical practitioners also gave authorisation for the participation of general practitioners.

### Measurement of anticholinergic effects

Cholinergic side effects, or anticholinergic burden, may be quantified (a) by means of a serum radioreceptor assay to quantify drug induced muscarinic blockade[13] [17] [18] or (b) by the summation of average estimated clinical effects of specific drugs.[19] The former has greater biological precision but is essentially a transient global measure that may not represent cerebral levels because of the differential permeability of the blood-brain barrier. Cognitive impairment and even delirium have been reported with several drugs despite serum concentrations being well within the normal limits.[20] The second method takes into account duration of exposure but assumes drugs to have additive properties.

For our study, we calculated an anticholinergic burden classification which combines both measures. From an extensive review of the literature we constructed a table associating known anticholinergic drugs with their serum anticholinergic activity where available, as

shown by radioreceptor assays. Given the limitations of this method in establishing clinically significant levels of serum anticholinergic activity, each participant's records were examined by a pharmacologist, physician, and biologist in order to classify the anticholinergic burden from 0 to 3 (0=no anticholinergic drugs used, 1=drugs used with no likely effect, 2=drugs used with low effect, 3=drugs used with high effect). Our classification uses measured serum anticholinergic activity but also takes into account mode of drug administration (topical, nasal, oral, etc), possible drug interaction effects, and potential blood-brain barrier permeability.[21] [22]

#### **Assessment of cognitive performance**

All participants annually received a computerised neuropsychometric examination, ECO (examen cognitif par ordinateur). This assesses primary memory, verbal and visuospatial secondary memory, language skills (word and syntax comprehension, naming, verbal fluency), visuospatial performance (ideational, ideo-motor, and constructive apraxia), functional and semantic categorisation of visual data (visual reasoning and form perception), and focused and divided attention (visual and auditory modalities). The development of the examination and the theoretical basis for test construction and validation is described elsewhere.[23] The following cognitive scores were used in the present study.

Reaction time—assessed by asking participants to touch a target on a tactile screen

Reasoning—assessed by a multiple choice task requiring completion of a logical visual series with increasingly complex decision rules

Attention—measured by response time on a dual task (simultaneous visual selection and counting of auditory stimuli)

Primary memory—assessed by immediate recall of a list of first names (verbal memory) and recall of a trail traced on the computer screen (spatial memory)

Secondary verbal and spatial memory—measured by delayed recall of proper names with and without semantic and phonetic cueing; delayed recall of faces associated with the proper names; and recall of two narratives, one with a logical sequence and the other a description

Implicit memory—recognition of the previously learnt proper names and distractors progressively built up by random pixels on the computer screen

Visuospatial ability—measured by the number of elements correct in the copying of complex meaningful and meaningless figures

Language—assessed by object naming and verbal fluency.

#### **Diagnoses of mild cognitive impairment and dementia**

Participants underwent a standardised neurological examination for the diagnosis of neuropsychogeriatric disorder, based on DSM-III-R criteria, carried out by a neurologist without knowledge of the results of the cognitive tests. At eight years, all surviving participants were contacted again for neurological assessment, and 80% were reassessed (loss

being principally due to mortality or change of address). In cases where assessment was not possible, we examined participants' medical records in collaboration with their general practitioner to determine a possible diagnosis of dementia.

Mild cognitive impairment was diagnosed according to the revised criteria proposed by the Stockholm consensus group.[2] They stipulate the presence of a complaint from either the patient or a family member, absence of dementia, change from normal functioning, decline in any area of cognitive functioning, and preserved overall general functioning but possibly with increasing difficulty in performing activities of daily living. In our study we defined the cognitive deficit as performance  $>1.5$  standard deviations below the mean score of the total population at baseline after taking into account age (classified by decade) and education (classified as no formal education or education to primary school level, secondary school level, or tertiary level).

### **Statistical methods**

We compared the cognitive performance of users and non-users of anticholinergic drugs at one-year follow-up by analysis of variance adjusted by age, sex, and education level. Conversion of raw scores to z scores (calculated using the mean and standard deviation in the sample) permitted direct comparison of performance of drug users and non-users across different tests. We used a logistic regression model to predict mild cognitive impairment at one-year follow-up by anticholinergic drugs use over the past year while taking account of other identified risk factors for cognitive impairment (age, sex, education, untreated depression, and treated hypertension). We analysed the data with SPSS, version 12.0.

## **Results**

### **Use of anticholinergic drugs**

Of the 372 elderly people recruited from general practices in the south of France, 51 (14%, 95% confidence interval 10% to 17%) were taking at least one anticholinergic drug at the start of the study (42 taking one anticholinergic drug and nine taking more than one). None was taking acetylcholinesterase inhibitors. At one-year follow-up, 30 of these 51 participants were still taking anticholinergic drugs regularly, 26 taking the same drug. Twenty one participants had stopped taking anticholinergic drugs during the year, while 24 had started taking them. The following analyses thus concerned the 297 participants who had taken no anticholinergic drugs at baseline or in the following year and the 30 (9%, 6% to 12%) who had used anticholinergic drugs throughout the year. Table 1 lists the drugs used and their estimated anticholinergic burden.



**Table 1** List of anticholinergic drugs used by study participants. All drugs had an anticholinergic burden classification of 3 (see Methods for details) unless stated otherwise

Compound	Drug class	Application
Aceprometazine	Neuroleptic, antihistamine (phenothiazine)	Psychiatry
Acepromazine	Neuroleptic (phenothiazine)	Psychiatry
Alimemazine*	Antihistamine, sedative (phenothiazine)	Allergy relief, psychiatry
Alprazolam	Anxiolytic (benzodiazepine)	Psychiatry
Alverine*	Antispasmodic	Analgesia and anti-inflammatory
Amitriptyline	Tricyclic antidepressant	Psychiatry
Amoxapine	Tricyclic antidepressant	Psychiatry
Belladonna alkaloids	Antispasmodic	Analgesia and anti-inflammatory
Chlorphenamine	Antihistamine	Analgesia and anti-inflammatory
Clomipramine	Tricyclic antidepressant	Psychiatry
Clorazepate	Anxiolytic (benzodiazepine)	Psychiatry
Codeine*	Analgesic, antipyretic	Analgesia and anti-inflammatory
Colchicine	Anti-hyperuricemic, anti-inflammatory	Rheumatology
Dexchlorpheniramine	Antihistamine	Allergy relief
Digoxin	Antiarrhythmic, cardiotonic	Cardiology
Furosemide	Diuretic, antihypertensive	Cardiology
Hydroxyzine	Anxiolytic, antihistamine	Psychiatry
Imipramine	Tricyclic antidepressant	Psychiatry
Levomepromazine	Neuroleptic (phenothiazine)	Psychiatry
Maprotiline	Tetracyclic antidepressant	Psychiatry
Opipramol	Tricyclic antidepressant	Psychiatry
Orphenadrine	Antiparkinsonian	Neurology
Oxybutynin	Antispasmodic	Urology
Theophylline*	Bronchodilator, antiasthmatic	Pneumology
Trihexyphenidyl	Antiparkinsonian	Neurology
Trimipramine	Tricyclic antidepressant	Psychiatry
Tropatepine	Antiparkinsonian	Neurology

\*Anticholinergic burden classification of 2.

The 30 consistent users of anticholinergic drugs were predominantly women (77%) and, compared with the 297 consistent non-users, were older (mean (SD) age 80.9 (8.0) v 74.8 (7.4) years,  $P < 0.001$ ) and less likely to have had tertiary education (10% v 19%).

### Assessment of cognitive performance

Table 2 compares the cognitive performance of the consistent users of anticholinergic drugs with that of the consistent non-users. The drug users showed significantly poorer simple reaction time, attention, immediate and delayed visuospatial memory, narrative recall, verbal fluency, and, to a lesser extent, object naming and visuospatial construction. A difference in immediate and delayed recall of names and name-face associations lost significance when adjusted for age, and the two groups showed no significant difference for implicit memory and logical reasoning.

**Table 2** Cognitive performance of consistent users of anticholinergic drugs and consistent non-users. Values are means (SD) test scores unless stated otherwise

Cognitive test	Non-users (n=297)	Users (n=30)	P value of difference*
Simple reaction time	13.4 (5.9)	19.4 (7.0)	<0.001
Logical reasoning	1.26 (1.0)	0.8 (0.8)	0.35
Attention (response time on dual task)	21.6 (5.6)	27.5 (10.2)	<0.001
Primary verbal memory (immediate recall of name list)	5.0 (1.6)	4.3 (1.9)	0.13
Secondary verbal and spatial memory:			
Delayed free recall of names	4.8 (2.0)	3.7 (2.3)	0.25
No of faces recalled	7.7 (1.5)	6.2 (1.8)	<0.001
Total No of correct name-face associations	2.8 (2.0)	1.5 (2.2)	0.12
Narrative recall total	24.3 (8.6)	16.8 (8.9)	<0.01
Implicit memory	2.2 (3.4)	1.8 (2.9)	0.51
Visuospatial ability:			
Visuospatial span	4.1 (1.9)	3.1 (1.3)	<0.01
Construction total	23.4 (2.1)	21.4 (4.4)	<0.01
Language:			
Naming total correct	9.3 (1.1)	8.3 (1.7)	<0.01
Fluency total	33.5 (11.4)	23.2 (11.6)	<0.001

\*Analysis of variance adjusted by age, sex, and education.



Conversion of raw scores to z scores permitted direct comparison of performance across different tests. The figure shows the mean z scores for the two groups. While the non-users of anticholinergic drugs showed a relatively even performance across the tests, the users not only performed worse but showed considerable variability in their cognitive profile.

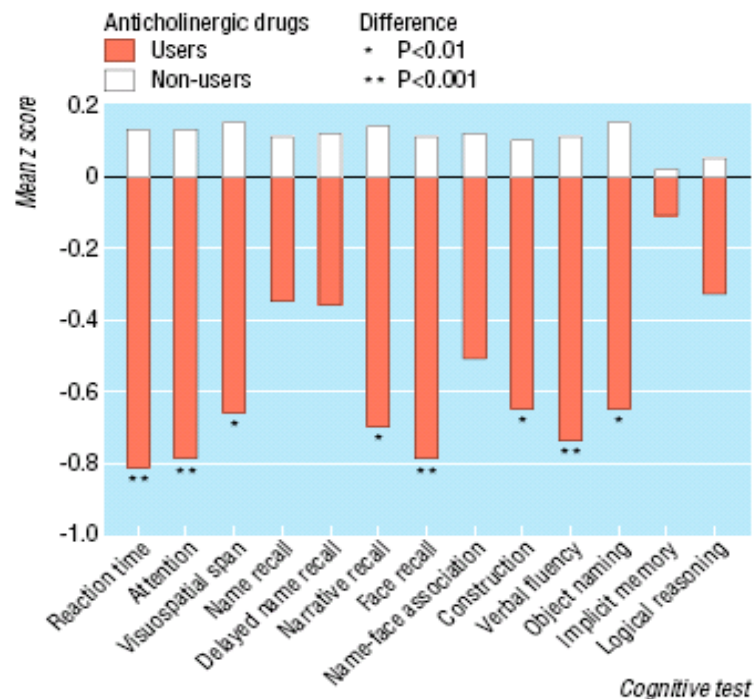


Figure: Mean z scores for 30 consistent users of anticholinergic drugs and 297 consistent non-users on tests of cognitive performance

A comparison of participants with a substantial anticholinergic burden (scoring 2 or 3 on our classification) with non-users of anticholinergic drugs showed that those with a burden score of 3 had poorer cognitive scores, but the differences between groups did not reach significance, possibly because of the small numbers of individuals.

#### Assessment of mild cognitive impairment

Among the 297 consistent non-users of anticholinergic drugs, mild cognitive impairment was diagnosed in 105 (35%, 95% confidence interval 30% to 41%). Among the 30 consistent users of anticholinergic drugs, however, 24 (80%, 66% to 94%) met the criteria for mild cognitive impairment, giving an attributable risk of 19%. To assess the extent to which a diagnosis of mild cognitive impairment was due to anticholinergic drug use, we created a logistic regression model to predict such a diagnosis at one-year follow-up, taking into

account anticholinergic drug use over the previous year and other identified risk factors for cognitive impairment (age, sex, education, untreated depression, treated hypertension). After adjustment for other possible causes of cognitive impairment, the only highly significant predictors of mild cognitive impairment were anticholinergic drug use (odds ratio 5.12, 1.94 to 13.51;  $P=0.001$ ) and age (1.09, 1.06 to 1.13,  $P<0.001$ ). The other possible risk factors lost significance when age and anticholinergic drugs use were entered into the model.

#### **Development of dementia**

Although the consistent users of anticholinergic drugs were significantly more likely have a diagnosis of mild cognitive impairment at one-year follow-up (80%) than consistent non-users (35%), we found no difference in overall dementia rates at eight-year follow-up between the drug users (16%) and non-users (14%). Small numbers of individuals made it impossible to make a statistical comparison of rates of conversion.

#### **Discussion**

In our sample of elderly people without dementia we found that those taking anticholinergic drugs showed specific cognitive deficits compared with non-users of anticholinergic drugs and were more likely to be classified as having mild cognitive impairment, but seemed no more likely to develop dementia.

#### **Anticholinergic drug use and cognitive performance**

Even after adjustment for confounding variables, the participants who used anticholinergic drugs had significantly poorer performance on psychomotor speed, primary and secondary visuospatial memory, narrative recall, and visuospatial construction than non-users. We found no significant difference for implicit memory or logical reasoning ability.

The performance of the drug users is in these respects similar to the cognitive performance seen in younger adults given scopolamine.[9] [10] However, we also found language performance to be affected, and name-face recall differences disappeared when adjusted for age. This difference with previous findings may be due in part to the tests used: auditory speech perception is affected by scopolamine,[24] and in our study the name-face tasks were presented visually whereas the narrative recall and verbal fluency tasks were presented orally. Studies with scopolamine also used a much narrower range of cognitive tasks than we did and did not control for age in elderly groups.

#### **Anticholinergic drug use and diagnosis of mild cognitive impairment and dementia**

In our sample 19% of subjects were classified as having mild cognitive impairment,[5] a rate similar to that observed in other studies.[3-6] Nineteen per cent of those with mild

cognitive impairment were consistent users of anticholinergic drugs; 80% of the drug users were classified as mildly cognitively impaired. Non-users of anticholinergic drugs were significantly less likely to be classified as having mild cognitive impairment, but no difference was found in dementia rates by eight years' follow-up between anticholinergic drug users (16%) and non-users (14%). These results suggest that elderly people using anticholinergic drugs are highly likely to be included as cases in population and clinical studies of mild cognitive impairment, that they represent a fifth of all cases of mild cognitive impairment, but are not at increased risk for dementia.

#### **Attributable risk**

The study participants who used anticholinergic drugs had poor cognitive performance in multiple domains, making them highly likely to be classified as mildly cognitively impaired, with an attributable risk of 19%. To what extent, however, can we directly attribute these cognitive deficits to anticholinergic drugs alone? Epidemiological studies have identified several important risk factors for mild cognitive impairment—age, education, treatment for hypertension, untreated depression, and apolipoprotein e4 allele—with age consistently identified as the principal risk.[25] [26] In our study we were able to take into account all of these factors (with the exception of apolipoprotein E, which was not available for all subjects), and we found anticholinergic drug use to be the most significant independent predictor of mild cognitive impairment.

#### **Conclusion**

About 10% of the elderly people in our general practice sample took anticholinergic drugs over an extended period, giving rise to multiple cognitive deficits and a high likelihood of being classified as mildly cognitively impaired, although the probability of evolution towards dementia was low. Given that the aim of identifying mild cognitive impairment is the early treatment of dementia, notably with acetylcholinesterase inhibitors, people with mild cognitive impairment due to anticholinergic drugs could be in the absurd situation of receiving pro-cholinergic drugs to counteract the effects of anticholinergic agents.

Our findings are relevant to both research on mild cognitive impairment, which should take into account the possibility that cases may be due to anticholinergic drug use, and to the clinical setting, where anticholinergic drugs should be considered as a possible reversible cause of mild cognitive impairment.

**What is already known on this topic**

Clinical studies show that anticholinergic agents may produce cognitive deficits in young adults similar to the cognitive deficits seen in elderly people

Elderly people are high consumers of drugs known to have anticholinergic effects

**What this study adds**

Elderly people taking anticholinergic drugs for more than a year had cognitive deficits similar to those shown by young adults given scopolamine

Eighty per cent of these people met the criteria for mild cognitive impairment

However, they were not at increased risk of developing dementia, suggesting treatment with acetylcholinesterase inhibitors would be inappropriate

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