Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study

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OBJECTIVES: To determine whether the use of medications with possible and definite anticholinergic activity increases the risk of cognitive impairment and mortality in older people and whether risk is cumulative.

DESIGN: A 2-year longitudinal study of participants enrolled in the Medical Research Council Cognitive Function and Ageing Study between 1991 and 1993.

SETTING: Community-dwelling and institutionalized participants.

PARTICIPANTS: Thirteen thousand four participants aged 65 and older.

MEASUREMENTS: Baseline use of possible or definite anticholinergics determined according to the Anticholinergic Cognitive Burden Scale and cognition determined using the Mini-Mental State Examination (MMSE). The main outcome measure was decline in the MMSE score at 2 years.

RESULTS: At baseline, 47% of the population used a medication with possible anticholinergic properties, and 4% used a drug with definite anticholinergic properties. After adjusting for age, sex, educational level, social class, number of nonanticholinergic medications, number of comorbid health conditions, and cognitive performance at baseline, use of medication with definite anticholinergic effects was associated with a 0.33-point greater decline in MMSE score (95% confidence interval (CI) = 0.03–0.64, $P = .03$) than not taking anticholinergics, whereas the use of possible anticholinergics at baseline was not associated with further decline (0.02, 95% CI = −0.14–0.11, $P = .79$). Two-year mortality was greater for those taking definite (OR = 1.68; 95% CI = 1.30–2.16; $P < .001$) and possible (OR = 1.56; 95% CI = 1.36–1.79; $P < .001$) anticholinergics.

CONCLUSION: The use of medications with anticholinergic activity increases the cumulative risk of cognitive impairment and mortality. **J Am Geriatr Soc 2011.**

Key words: anticholinergic activity; cognitive impairment; elderly

Identifying risk factors for cognitive decline may lead researchers to a better understanding of clinical interventions to reduce the risk of developing Alzheimer's disease. Less physical, cognitive, and social activity and the presence of diabetes mellitus, hypertension, and hyperlipidemia have been identified as potentially modifiable risk factors for cognitive decline, including incident dementing illnesses such as Alzheimer's disease.[1] Use of anticholinergic medications has been associated with acute cognitive impairment.[2–7] Animal models[8–10] link direct antagonism of the muscarinic cholinergic receptor M1 to decline in cognitive function, but there have been few studies evaluating the long-term exposure to medications as a modifiable risk factor. Progression of Alzheimer's-type pathology may be amplified with M_1 blockade,[11] whereas enhancing

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cholinergic transmission through the M_1 receptor may reduce the deposits of Aβ peptides.[12,13]

A recently published systematic review of the association between the anticholinergic activity of medications and cognitive function found a strong link between acute cognitive impairment and anticholinergic potency of medications as measured according to the serum anticholinergic assay or through consensus opinion,[14] but the review did not identify sufficient studies that examined the long-term cognitive effects of anticholinergics.[14] Therefore, data from an ongoing observational study (Medical Research Council Cognitive Function and Ageing Study; MRC CFAS) were examined to support or refute the hypothesis that the use of medications with possible and definite anticholinergic activity increases the risk of cognitive impairment and death in older people and to determine whether there is a cumulative effect.

METHODS

Study Participants

Participants included in this analysis underwent the baseline screening interview of the MRC CFAS—a prospective community-based epidemiological study of random samples of people aged 65 and older. The study has been described elsewhere.[15,16] In summary, at each of the five study centers in England and Wales, approximately 2,500 people agreed to a structured interview to collect sociodemographic information, cognitive measures (including the Mini-Mental State Examination (MMSE)), medication, and activities of daily living. Participants were sampled from general practice lists, and so are representative of the population aged 65 and older living at home and in institutions. MRC CFAS has ethical approval from the Eastern Anglia Multicentre Research Ethics Committee and all local ethical committees for the duration of the study (1990 to date).

Measurement of Cognition

Each participant was administered the MMSE at baseline screening and at the follow-up assessment.

Ascertainment of Mortality

All participants in MRC CFAS were flagged on the UK Office of National Statistics National Health Service Central Register to enable routine collection of mortality information.

Measuring Exposure to Anticholinergics

For the purposes of this study, each participant's anticholinergic burden was calculated using the Anticholinergic Cognitive Burden Scale (ACB).[3] The scale was developed through a systematic review of the literature to identify drugs with documented anticholinergic activity. Content validity was tested by presenting the list to an expert interdisciplinary panel of geriatricians, pharmacists, geriatric psychiatrists, general physicians, specialist geriatric nurses, and aging brain researchers. Any disagreements were resolved by consensus.

Medications were identified to have absent, possible, or definite anticholinergic properties based on the ACB.[3,14] Drugs with possible anticholinergic effects were defined as those with serum anticholinergic activity or in vitro affinity to muscarinic receptors but with no known clinically relevant negative cognitive effects (ACB score = 1). Drugs with established and clinically relevant cognitive anticholinergic effects were considered to be definite anticholinergics (ACB score 2–3).[3,14] Using the ACB, a team of a pharmacist (IM), a physician (DS), and a geriatric psychiatrist (CF) independently reviewed all medications used by the study population and categorized medications into three categories: absent anticholinergic activity (ACB score = 0), possible anticholinergic activity (ACB score = 1), or definite anticholinergic activity (ACB score = 2 or 3). The scores were then compared to reach a consensus agreement on the ACB of each medication that participants in the CFAS had taken. An additional variable was structured to capture the total burden of anticholinergic per participant by adding the score of each possible or definite anticholinergic.

Measurement of Medication Use and Covariates

Details of prescription and over-the-counter medication reporting and associations at baseline have been described previously.[17] In brief, trained interviewers assessed the participants' current use of medication with the question: "Do you take any medicine, tablets or injections of any kind, either that you buy yourself or that are prescribed by your doctor?" Drug name, dose, frequency, and quantity were recorded for each reported medication. To improve data accuracy, interviewers were required when possible to see the medicines or consult the matron in nursing homes and to check exactly which medication was taken before entering the data. The medication data were coded according to the Read Codes Drug and Appliance Dictionary, Version 2.[18] Using this coding, medications were also grouped into the following classes for analysis: gastrointestinal, cardiovascular, respiratory, central nervous system excluding antipsychotics, antipsychotics, urinary tract infection, and other.

Covariates investigated from the baseline survey were sex, age, institutionalization (residential care including nursing homes and long-stay hospitals), social class (highest occupation class achieved during working life or that of the husband in the case of housewives—professional or managerial, skilled, or partly skilled or unskilled), years of full-time education, smoking status (never, past, current), and alcohol drinker (ever, never). The number of self-reported health conditions from the following was also examined: angina pectoris, arthritis, asthma, bronchitis, depression, diabetes mellitus, epilepsy, heart attack, high blood pressure, Parkinson's disease, pernicious anemia, stroke, and thyroid problems.

Statistical Analysis

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for factors predicting anticholinergic medication use at baseline. Backward stepwise regression, retaining variables with $P < .15$, was used to build a multivariable logistic model to identify independent predictors of anticholinergic medication use. After this regression, all subsequent analyses were adjusted for age,

sex, education, social class, number of self-reported health conditions, and nonanticholinergic medications.

Analysis of Cognition

Baseline MMSE score and change in MMSE by 2-year follow-up were modeled using linear regression. For each analysis, the relationship with ACB score was included in three ways: categorical sum of ACB (*P*-value given for trend test), continuous sum of ACB, and any definite or possible anticholinergic medications. Owing to the ceiling effects, decline in MMSE is heavily dependent on baseline scores, so baseline MMSE scores were adjusted for in the longitudinal analysis. To test whether the effect varied with varying levels of cognitive impairment, results were further stratified according to MMSE score at baseline (0–21, 22–25, and 26–30).

Loss to Follow-Up

Logistic regression was also used to measure the association between ACB score and loss to follow-up through dropout and mortality by 2 years after adjusting for the potential covariates and baseline MMSE score.

Version 8.3 of the MRC CFAS data was used, and STATA 10 (StataCorp., College Station, TX) was used for the analysis.

RESULTS

Of the 13,004 participants at baseline in MRC CFAS, 12,423 (96%) provided data on medication use. Sixty percent of the population with medication data were women, and mean age at baseline was 75.2 ± 6.8. MMSE at baseline was complete for 12,250 (99%) participants. The mean score was 25.9 ± 3.5 (median 27, interquartile range 24–28). Ten percent of participants had a MMSE score of 0–21, 25% of 22–25, and 65% of 26–30. Of the 12,250 participants with complete medication data and MMSE score at baseline, by 2-year follow-up, 1,223 (10%) had died, 2,493 (20%) had dropped out, and 8,534 had completed the 2-year follow-up survey (8,334 with complete MMSE).

Anticholinergic Medication Use

Of the baseline sample, 9,850 (79%) participants reported taking any medication and 6,010 (48%) were taking medications with possible or definite anticholinergic properties (ACB score ≥1), of whom 508 were taking medication with definite anticholinergic properties (ACB score ≥2). The most frequently reported anticholinergic medications were furosemide (n = 1,384), dextropropoxyphene (n = 955), atenolol (n = 922), and nifedipine (n = 752). Each of these was rated as having possible anticholinergic properties (ACB score = 1). The most frequent medication with moderate activity (ACB = 2) was carbamazepine (n = 69), and the most frequent medication with severe activity (ACB = 3) was amitriptyline (n = 136). For those taking anticholinergic medications, mean total ACB score was 1.8 ± 1.1 (maximum 12).

Exposure to any anticholinergic medication was independently associated with older age, lower social class, former smoking, and more health conditions (Table 1). Women were more likely to report taking anticholinergic medications, but the greater number of health conditions that women reported explained this. Participants living in institutions were more likely to report taking anticholinergic medications, but their older age explained this.

Association Between Anticholinergic Medication Use and Cognition at Baseline

A dose-response relationship was observed between greater total ACB score and lower MMSE, with those who scored 5 or higher on the ACB having a mean MMSE score of 25.0 ± 3.7, compared with 26.1 ± 3.5 in those taking no anticholinergic medications (Table 2). In multivariable analysis, this relationship was largely unaltered, with a total ACB score of 5 or higher associated with an MMSE score of 0.70 points lower (95% CI = 0.25–1.16) than for no anticholinergics ($P < .001$). Taking any definite anticholinergic medication was also associated with an MMSE score 0.82 points lower (95% CI = 0.55–1.10) than for no anticholinergic medications. No association between taking possible anticholinergic medications and MMSE score at baseline was observed.

Association Between Anticholinergic Medication and Cognitive Decline

For the 8,334 participants with an MMSE score recorded at the 2-year follow-up, the average baseline and 2-year MMSE scores were 26.5 ± 3.1 and 25.8 ± 4.0, respectively. The change in scores were approximately normally distributed, with participants dropping on average 0.8 ± 2.9 points in the 2 years. Table 3 shows the effect of anticholinergic medication use on decline in MMSE at 2 years stratified according to MMSE severity group at baseline adjusted for age, sex, baseline MMSE score, education, social class, number of nonanticholinergic medications, and number of health conditions. A dose-response relation was observed between greater total ACB score and MMSE decline, with those who scored 4 or greater on the ACB declining by 0.34 (95% CI = 0.01–0.67) more points on the MMSE than those not taking anticholinergics. Taking any definite anticholinergics was also associated with declining by 0.33 (95% CI 0.03–0.64) more points on the MMSE than those taking no anticholinergics.

The greatest effect on cognitive decline was seen in the group with a baseline MMSE score of 26 to 30. Taking any definite anticholinergic medication was associated with a decline of 0.52 (95% CI = 0.21–0.83) more points on the MMSE than those not taking definite anticholinergics in this group. Similar effects were seen in the group with a baseline MMSE score of 22 to 25 but not in the group with a baseline MMSE score of 0 to 21, although the numbers in this group were small (Table 3).

Association Between Anticholinergic Medication Use and Mortality and Attrition

After adjusting for age, sex, baseline MMSE score, education, social class, number of nonanticholinergic medications, and number of health conditions, taking anticholinergic medications was associated with death at 2 years, with a dose-response effect on ACB score. Ninety-eight (20%) of those who scored 4 or greater on the ACB and 436 (7%) of those not taking anticholinergics had died during the 2-year follow-up. For every additional point scored on the ACB, the odds of dying increased by 26%

Table 1. Predictors of Anticholinergic Medication Use (N = 12,423)

Predictor	Anticholinergic Use (n)	Percent with Anticholinergic Use N	Univariable Results		Multivariable Results	
			Odds Ratio (95% CI)	*P*-Value	Odds Ratio (95% CI)	*P*-Value
Sex						
Male	2,317	5,003 (46)	1.00		NA	
Female	3,693	7,420 (50)	1.15 (1.07 to 1.23)	<.001		
Age						
65–69	1,310	3,132 (42)	1.00	<.001	1.00	<.001
70–74	1,433	3,088 (46)	1.20 (1.09 to 1.33)		1.18 (1.06 to 1.31)	
75–79	1,448	2,819 (51)	1.47 (1.33 to 1.63)		1.45 (1.30 to 1.62)	
≥80	1,819	3,384 (54)	1.62 (1.47 to 1.78)		1.67 (1.49 to 1.86)	
Education, years						
<9	429	875 (49)	1.00	.002	NA	
9–10	4,083	8,265 (49)	1.02 (0.88 to 1.17)			
>10	1,454	3,181 (46)	0.88 (0.75 to 1.02)			
Unknown	44	102 (43)	0.79 (0.52 to 1.19)			
Social class*						
Professional or managerial	1,665	3,714 (45)	1.00	<.001	1.00	.003
Skilled	2,934	5,902 (50)	1.22 (1.12 to 1.32)		1.17 (1.07 to 1.28)	
Partly skilled or unskilled	1,330	2,634 (50)	1.26 (1.14 to 1.39)		1.17 (1.05 to 1.31)	
Unknown	81	173 (47)	1.08 (0.80 to 1.47)		1.13 (0.79 to 1.61)	
Smoking status						
Never	2,044	4,254 (48)	1.00	<.001		<.001
Former	2,959	5,790 (51)	1.13 (1.04 to 1.22)		1.11 (1.02 to 1.21)	
Current	989	2,338 (42)	0.79 (0.72 to 0.88)		0.88 (0.79 to 0.99)	
Alcohol intake						
Never	751	1,474 (51)	1.00		NA	
Ever	5,241	10,910 (48)	0.89 (0.80 to 0.99)	.04		
Institutionalized						
No	5,743	11,916 (48)	1.00		NA	
Yes	266	506 (53)	1.19 (1.00 to 1.42)	.05		
Number of comorbidities†						
0	477	2,390 (20)	1.00	<.001	1.00	<.001
1	1,547	3,882 (40)	2.66 (2.36 to 2.99)		2.63 (2.34 to 2.97)	
2	1,793	3,134 (57)	5.36 (4.74 to 6.06)		5.36 (4.73 to 6.06)	
3+	2,142	2,918 (73)	11.07 (9.72 to 12.60)		10.96 (9.61 to 12.48)	

* Defined according to the highest occupation class achieved during working life of the head of household.

† Number of self-reported comorbidities: heart attack, diabetes mellitus, bronchitis, stroke, arthritis, asthma, angina pectoris, hypertension, epilepsy, thyroid problems, Parkinson's disease, pernicious anemia, and depression.

(OR = 1.26, 95% CI = 1.20–1.32). The effect was present for the use of definite (OR = 1.68, 95% CI = 1.30–2.16) and possible (OR = 1.56, 95% CI = 1.36–1.79) anticholinergics. Results were also found not to vary according to baseline MMSE group (results not shown). There was no association between dropout rate and ACB (results not shown).

DISCUSSION

In this large prospective study, 48% of patients reported taking medications with anticholinergic properties. Overall, the results in participants with normal or mildly impaired cognitive function at baseline support the hypothesis that medications with a definite anticholinergic effect are independently associated with greater risk of cognitive decline and mortality over 2 years. Although no evidence of an association between anticholinergic use and cognitive decline in those with already significantly impaired cognition (MMSE score < 22) was found, 24% of this group died before follow-up assessment, and mortality was strongly related to ACB. It is therefore possible that cognitive decline associated with anticholinergic medication use occurred in this group before death but was not captured in the study.

These results confirm the suggestion that anticholinergics adversely affect cognitive abilities.[6,7,19–25] Most of the other similar population-based data support a link between cognitive decline and use of anticholinergics. One of the largest other studies, involving 6,912 participants aged 65 and older, found greater risk of cognitive decline and dementia, which decreased if anticholinergics were discontinued.[7] In a longitudinal study involving 372

Table 2. Association Between Anticholinergic Medication Use and Mini-Mental State Examination (MMSE) Score at Baseline (N = 12,250)

			MMSE		Adjusted MMSE Difference*	
ACB Measure	n	%	Mean ± Standard Deviation	Median (Interquartile Range)	Estimate (95% Confidence Interval)	*P*-Value
Model 1						
Sum of ACB score						
0	6,327	52	26.1 ± 3.5	27 (24–29)	0.00	.001
1	3,273	27	25.8 ± 3.4	27 (24–28)	− 0.03 (− 0.11 to 0.16)	
2	1,441	12	25.6 ± 3.6	26 (24–28)	0.09 (− 0.27 to 0.10)	
3	719	6	25.6 ± 3.6	26 (24–28)	0.10 (− 0.35 to 0.14)	
4	306	2	25.1 ± 3.9	26 (23–28)	0.55 (− 0.91 to − 0.19)	
≥5	184	2	25.0 ± 3.7	26 (23–28)	0.70 (− 1.16 to − 0.25)	
Model 2						
Sum of ACB (per point)	12,250	100	25.9 ± 3.5	27 (24–28)	− 0.09 (− 0.14 to − 0.04)	<.001
Model 3						
Any anticholinergic drugs						
Possible						
No	6,541	53	26.1 ± 3.5	27 (24–28)	0.00	.71
Yes	5,709	47	25.7 ± 3.5	27 (24–28)	0.02 (− 0.10 to 0.14)	
Definite						
No	11,742	96	25.9 ± 3.5	27 (24–28)	0.00	<.001
Yes	508	4	24.9 ± 3.9	27 (23–28)	− 0.82 (− 1.10 to − 0.55)	

* Adjusted for age, sex, education, social class, number of nonanticholinergic medications, and number of comorbidities.
ACB = Anticholinergic Cognitive Burden Scale.

elderly people, after adjustment for other causes of cognitive impairment, anticholinergic use was a highly significant predictor of mild cognitive impairment (MCI) (OR = 5.12, 95% CI = 1.94–13.51).[23] Consistent anticholinergic users were significantly more likely to develop MCI at 1 year (80%) than consistent nonusers (35%); there were no differences in overall dementia rates (16% vs 14%) at 8 years.[23] A study of 836 older people found that participants with dementia who were taking donepezil were more likely to use anticholinergics than matched controls not taking

Table 3. Association Between Anticholinergic Medication Use and Additional Decline on the Mini-Mental State Examination (MMSE) at 2 Years Stratified According to MMSE Score at Baseline

	Baseline MMSE							
	26–30 (n = 6,041)		22–25 (n = 1,769)		0–21 (n = 524)		Overall	
ACB Measure	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value	Estimate (95% CI)	*P*-Value
Model 1								
Sum of ACB score								
0	0.00	.02	0.00	.03	0.00	.11	0.00	.09
1	0.05 (− 0.08 to 0.19)		− 0.06 (− 0.45 to 0.32)		0.33 (− 0.60 to 1.27)		0.03 (− 0.11 to 0.17)	
2	0.01 (− 0.19 to 0.21)		0.01 (− 0.53 to 0.54)		− 0.09 (− 1.31 to 1.14)		0.01 (− 0.20 to 0.21)	
3	− 0.21 (− 0.47 to 0.05)		− 0.28 (− 1.00 to 0.45)		0.97 (− 0.70 to 2.65)		− 0.15 (− 0.42 to 0.12)	
4+	− 0.51 (− 0.84 to − 0.18)		− 0.44 (− 1.24 to 0.36)		1.85 (− 0.18 to 3.87)		− 0.34 (− 0.67 to − 0.01)	
Model 2								
Sum of ACB score								
Per point	− 0.07 (− 0.13 to − 0.02)	.01	− 0.07 (− 0.21 to 0.07)	.32	0.32 (− 0.02 to 0.65)	.07	− 0.05 (− 0.10 to 0.01)	.10
Model 3								
Any anticholinergic drugs								
Possible (1)	0.02 (− 0.10 to 0.14)	.75	− 0.05 (− 0.39 to 0.29)	.77	0.38 (− 0.43 to 1.20)	.35	0.02 (− 0.11 to 0.14)	.79
Definite (2–3)	− 0.52 (− 0.83 to − 0.21)	<.001	− 0.32 (− 1.10 to 0.46)	.42	1.10 (− 0.61 to 2.82)	.21	− 0.33 (− 0.64 to − 0.03)	.03

Models adjusted for age, sex, baseline MMSE, education, social class, number of non-anticholinergic medications, and number of comorbidities.

donepezil (33.0% vs 23.4%; $P = .001$).[24] Definite anticholinergic use increased the risk of cognitive impairment, but not dementia, in a cohort of African Americans with normal cognitive function at baseline.[6] A longitudinal study of an elderly cohort found that anticholinergic use did not accelerate the rate of decline in cognitive status,[25] although this study used a binary independent variable—receiving or not receiving anticholinergics—and did not consider the effect of exposure to multiple anticholinergics, potentially underestimating the effect.[25]

The current study adds to the existing work evaluating anticholinergic exposure and cognitive impairment; in particular a dose-response effect for anticholinergic load and MMSE errors was demonstrated. Clinicians, therefore, need to review cumulative anticholinergic burden in people presenting with cognitive impairment. Also, as far as the authors are aware, this is the first team to identify a link between mortality and anticholinergic burden, although this finding should be treated with caution, because medications with possible anticholinergic effects are used for many diseases, such as hypertension[26] and congestive heart failure.[27] Therefore, the finding may simply reflect the prevalence of anticholinergic prescribing in disease states with significant morbidity.

STUDY STRENGTHS

The study has four important strengths. First, the population was large (N = 13,004) and representative of the older population of England and Wales. Second, the great majority of respondents reported medication data (96%), and detailed assessments of medication use allowed for accurate cross-sectional collection of medications that a participant may have in their home, including over-the-counter, herbal, and supplement products. Third, the comprehensive interview included cognitive assessment and ascertainment of many sociodemographic and health-related factors, allowing the independent effect of anticholinergic medications to be fully explored. Fourth, the use of the ACB has been validated elsewhere,[6,14] making the assessment of anticholinergic burden robust and clinically relevant.

STUDY LIMITATIONS

A limitation of the study is that it is unknown whether participants continued to take their medication with anticholinergic activity over the 2-year period, although it was possible to examine ACB score at 2-year follow-up in the main arm of the study (n = 6,685), which indicated that the ACB scores were stable over that period; for those not taking anticholinergics at baseline, 21% were incident users 2 years later, and for those taking anticholinergics at baseline, 17% were no longer users by the 2 year follow-up. The issues of compliance, duration, interrupted use, and the effect of different doses also require consideration, and there is, therefore, need for further work in this area. A future study should investigate the relationship between longitudinal cumulative actual anticholinergic exposure and cognitive decline. The medication from the database should be compared with potentially more-comprehensive methods of measuring medication utilization, such as dispensing records, that may better assess long-term exposure to anticholinergic medications. Adherence should be assessed in interviews and a random subsample of pill counts to validate the interviews.

The ACB has not been validated against in vitro measures of anticholinergic activity, although it is uncertain whether assays reflect actual in vivo anticholinergic activity in the human brain, and not all relevant drugs have been assayed in vitro, in particular drug metabolites, which may possess anticholinergic effects.[3,14,28,29]

Participants, who did not report their medications (4%) and those who could not complete the MMSE at baseline (1%) were excluded, but these numbers were small and unlikely to have affected the results. In addition no association was observed between baseline ACB score and dropout or missing 2-year MMSE.

This study could not consider subclinical disease, which may confound any associations, but medication use is associated with health status, so despite adjusting for many health-related factors, the possibility of residual confounding between health status and cognitive function cannot be excluded. Indication bias may have limited this study in that participants with cognitive impairment may have been more likely to be exposed to anticholinergic medications because of the presence of cognitive impairment.

CONCLUSION

This large population-based study showed that the use of medications with anticholinergic activity increased the risk of cognitive decline, as measured by the MMSE, and mortality over 2 years in participants with normal or mildly impaired cognition. With a growing prevalence of cognitive impairment in the older adult population, prescribers should be aware of the potential effect that anticholinergics have on the development of cognitive and executive dysfunction and mortality. Further research is needed to confirm and extend these findings, in particular the effect on mortality of anticholinergic burden and of different doses of medicines with anticholinergic activity.

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Author Contributions: Dr. Fox and all coauthors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Fox: design, interpretation, and manuscript preparation. Miss Richardson: analysis, manuscript preparation, and setting up the CFAS ACB medication database. Ian Maidment: project delivery, manuscript design, writing, drafting, and editing. Dr. Savva and Dr. Matthews: analysis and manuscript preparation. Dr. Smithard: medication review and manuscript preparation. Professor Coulton: study design

and manuscript preparation. Professor Katona and Professor Brayne: interpretation of findings and manuscript preparation. Dr. Boustani: medication review and manuscript preparation.

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