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Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

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Abstract

IMPORTANCE—Many medications have anticholinergic effects. The general view is that anticholinergic-induced cognitive impairment is reversible upon medication discontinuation. However, a few studies suggest that anticholinergic medications may be associated with increased dementia risk.

OBJECTIVE—To examine whether cumulative anticholinergic medication use is associated with a higher risk of incident dementia.

DESIGN—Prospective population-based cohort study using data from the Adult Changes in Thought Study.

SETTING—Group Health, an integrated health-care delivery system, Seattle, Washington

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Access to data: Dr. Gray and Ms. Anderson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Ms. Anderson conducted and was responsible for the data analysis.

PARTICIPANTS—3,434 participants aged 65 and older with no dementia at study entry. Initial recruitment occurred between 1994 and 1996 or 2000 and 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants received follow-up every two years.

EXPOSURE—Using computerized pharmacy dispensing data, cumulative anticholinergic exposure was defined as the total standardized daily doses (TSDD) dispensed in the past 10 years. The most recent 12 months of use was excluded to avoid use related to prodromal symptoms. Cumulative exposure was time-varying.

MAIN OUTCOMES AND MEASURES—Incident dementia and Alzheimer's disease using standard diagnostic criteria. Statistical analyses used Cox proportional hazards models, adjusted for demographic, health behaviors and health status including comorbidities.

RESULTS—The most common anticholinergic drug classes used were tricyclic antidepressants, first generation antihistamines and bladder antimuscarinics. Over a mean follow-up of 7.3 years, 797 participants (23%) developed dementia (637 developed Alzheimer's). A 10-year cumulative dose-response relationship was observed for both dementia and Alzheimer's disease (test for trend, $p<0.001$). For dementia, adjusted hazard ratios (HRs) and 95% confidence interval (CI) for cumulative anticholinergic use was 0.92 (95% CI, 0.74-1.16) for 1-90 TSDD; 1.19 (CI, 0.94-1.51) for 91-365 TSDD; 1.23 (CI, 0.94-1.62) for 366-1095 TSDD; and 1.54 (95% CI, 1.21-1.96) for >1095 TSDD, compared to non-use. A similar pattern of results was noted for Alzheimer's disease. Results were robust to secondary, sensitivity and post-hoc analyses.

CONCLUSION AND RELEVANCE—Higher cumulative anticholinergic medication use is associated with an increased risk for dementia. Efforts to increase awareness among health professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.

Keywords

dementia; Alzheimer disease; pharmacoepidemiology; cohort study; anticholinergic medication use; aged

INTRODUCTION

Medications with anticholinergic activity are widely used by older adults for diverse conditions such as overactive bladder, seasonal allergies, and depression. Some anticholinergic medications achieve the intended therapeutic effect by blocking the effect of acetylcholine at the muscarinic receptor within specific organ systems (e.g gastrointestinal antispasmodics, bladder antimuscarinics, antiparkinson agents). However, other medications have unintended anticholinergic effects that are not the primary therapeutic activity (e.g first generation antihistamines, tricyclic antidepressants, and certain antipsychotics).

The prevalence of anticholinergic medication use in older adults ranges from 8-37%.[1-5] This frequent use is despite professional organizations concluding that the benefits of using these agents in older adults may be outweighed by risks.[6-8] A well-known risk with anticholinergic medications is acute impairment in specific aspects of cognition (e.g., working memory, attention, psychomotor speed) which has been demonstrated in single

dose experimental studies [9-12] and cohort studies.[13] In addition, anticholinergics may be associated with global cognitive impairment.[13] Older adults may be more sensitive to anticholinergic effects in the central nervous system because of age-related changes in pharmacokinetics and pharmacodynamics, reduced acetylcholine mediated transmission in the brain, and increased permeability of the blood-brain barrier.[7]

The general view is that anticholinergic-induced cognitive impairment is reversible upon medication discontinuation. However, several investigators have reported that anticholinergic medications may be associated with increased risk for sustained cognitive deficits such as mild cognitive impairment or dementia.[1,2,14] One biologically plausible mechanism for these findings is that cumulative use of these agents result in abnormal brain pathology similar to that observed with Alzheimer's Disease (AD).[15] These observational studies have four important limitations. First, current anticholinergic use was only ascertained at study entry and periodically during follow-up by conducting a medication inventory. [1,14] Secondly, these studies lacked information about both the dose and duration of anticholinergic use. Thirdly, these studies had short follow-up periods. This later point is important as the pathophysiological changes in the brain of people with AD require several years to occur.[16] Finally, these studies did not take into account that certain anticholinergics are used to manage insomnia and depression, two prodromal conditions that can be seen in early but undiagnosed dementia, leading to protopathic bias.[17-19] In this situation, the association between anticholinergics and dementia would not be causal, but would arise because anticholinergics are used to treat early symptoms (e.g. prodromal) of dementia. Given the potentially enormous public health implications, a better understanding of the potential risks of cumulative anticholinergic use is needed.

The objective of this study was to examine the association between 10-year cumulative anticholinergic use and risk of dementia. We hypothesized that greater cumulative use of anticholinergics would be associated with increased risk.

METHODS

Design, Study Setting, and Participants

This population-based prospective cohort study was conducted within Group Health (GH), an integrated health-care delivery system in the northwest US. Participants were from the Adult Changes in Thought (ACT) study and details about study procedures have been detailed elsewhere.[20] Briefly, study participants aged 65 years and older were randomly sampled from Seattle-area GH members. Participants with dementia were excluded. The original cohort of 2,581 participants was enrolled between 1994 and 1996. An additional 811 participants were enrolled between 2000 and 2003. In 2004 the study began continuous enrollment to replace those who die or drop out. Participants were assessed at study entry and returned biennially to evaluate cognitive function and collect demographic characteristics, medical history, health behaviors and health status. The current study sample was limited to participants with at least 10 years of GH health plan enrollment prior to study entry to permit sufficient and equal ascertainment of cumulative anticholinergic exposure. The study sample was further limited to those with at least one follow-up study visit, as this is necessary to detect incident dementia. Of the 4,724 participants enrolled in ACT, 3,434

were eligible for the current study (2 withdrew consent to use GH data for research, 674 had less than 10 years of GH enrollment and 614 had no follow-up visits). Data through Sept 2012 were included in these analyses. The research protocol for this study was reviewed and approved by the GH and University of Washington's institutional review boards.

Identification of Dementia and Alzheimer Disease

The Cognitive Abilities Screening Instrument (CASI) was used to screen for dementia at study entry and each biennial study visit.[21] CASI scores range from 0 to 100 with higher scores indicating better cognitive performance. Participants with CASI scores of 85 or less (sensitivity 96.5%; specificity 92%)[22] underwent a standardized dementia diagnostic evaluation, including a physical and neurological examination by a study neurologist, geriatrician or internist, and a battery of neuropsychological testing. The results of these evaluations and laboratory testing, along with clinical data from participants' medical records, were then reviewed in a multidisciplinary consensus conference. The diagnoses of dementia and AD were made using research based criteria.[23,24] The date of dementia diagnosis was assigned as the midpoint between the ACT study visit where the diagnosis was made and the preceding visit. Participants with new onset dementia underwent at least one annual follow-up examination to confirm the dementia diagnosis.

Anticholinergic Medication Use

Medication use was ascertained from GH computerized pharmacy dispensing data that included drug name, strength, route of administration, date dispensed, and amount dispensed for each drug. Anticholinergic use was defined as those medications deemed to have strong anticholinergic activity as per consensus by an expert panel of health care professionals.[8,13] Since we were drawing on medication data from as early as 1984 (e.g. extending back 10 years prior to study entry), it was necessary to enhance this contemporary list with medications no longer on the market. Therefore, two clinician/investigators (SLG, JTH) reviewed previously published standard pharmacology/pharmacotherapy reference books to identify additional anticholinergic medications.[25,26] eTable 1 lists the strong anticholinergic medications according to medication class (e.g., first generation antihistamines, tertiary tricyclic antidepressants, bladder antimuscarinics).

To create our exposure measures, we first calculated the total medication dose for each prescription fill by multiplying the tablet strength by the number of tablets dispensed. This product was then converted to a standardized daily dose (SDD) by dividing by the minimum effective dose per day recommended for use in older adults according to a well-respected geriatric pharmacy reference (eTable 1).[27] For each participant, we summed the SDD for all anticholinergic pharmacy fills during the exposure period to create a cumulative total standardized daily dose (TSDD) (see example calculation in eFigure 1). This previously published method allows for standardized conversion of doses of different anticholinergic medications into a single exposure measure so that we are able to capture overall anticholinergic burden.[28,29]

The primary measure of anticholinergic use was 10-year cumulative exposure (eFigure 2). Prescription fills in the most recent 1 year period were excluded because of concern about

protopathic bias.[30] Our exposure was time-varying; we assessed 10-year cumulative exposure at study entry and updated the exposure as participants were followed forward in time. We categorized cumulative exposure as no use, 1-90 days, 91-365 days, 366-1095 days, or >1095 days (i.e. >3 years), with cut-points based on clinical interpretability and the exposure distribution observed in our sample. As an example, a person would reach the heaviest level of exposure if they took any of the following medications daily for more than 3 years: oxybutynin 5 mg, chlorpheniramine 4 mg, olanzapine 2.5 mg, meclizine 25 mg or doxepin 10 mg.

Covariates

Based on literature review we selected covariates that may confound the relationship between anticholinergic medication use and dementia.[13,14] Information about covariates came from standardized questionnaires that were administered by research staff at each study visit or GH electronic health databases. Demographic factors included age, sex, and years of education (at least some college vs not). Body mass index (BMI) was calculated from measured weight and height (i.e., underweight = <18.5, normal weight = 18.5–24.9, overweight = 25–29.9, obese = BMI of 30 or greater).[31] Participants were asked about current smoking status and whether they engaged in regular exercise (self-report of performing one of several listed activities for at least 15 minutes, at least three times per week).[32] For health status, we created dichotomous variables for self-rated health status (fair/poor vs better) and specific comorbidities including medication-treated hypertension and diabetes (computerized pharmacy data), history of stroke (i.e., self-report or International Classification of Diseases, version 9 codes 430.X, 431.X, 432.X, 434.X, 436.X and 438.X), and coronary heart disease (i.e., self-reported history of heart attack, angina, angioplasty, or coronary artery bypass surgery). *APOE* status was categorized as the presence or absence of any ε4 alleles.[33,34]

We also adjusted for medical indications associated with anticholinergic use to account for bias due to confounding by indication such as self-reported history of Parkinson's disease, high depressive symptoms (i.e., score of 10 or higher on the short version of the Center for Epidemiologic Studies Depression [CES-D] scale)[35] and current benzodiazepine use (computerized pharmacy data) as a proxy for sleep or anxiety disorders.

Statistical Analyses

We used multivariable Cox proportional hazards models with participant's age as the time scale[36] to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between anticholinergic medication use and incident dementia or possible/probable AD. Participants were censored at the earlier of their last ACT visit, disenrollment from the health plan GH or death if they did not have a dementia diagnosis. In addition, for the AD analysis, individuals were censored at the time of the dementia diagnosis that was not attributed to possible or probable AD. Separate models were fit for each outcome. Coronary heart disease, stroke, history of depressive symptoms, and current benzodiazepine use were entered as time-varying measures. Values at study entry were used for all other covariates. We conducted a complete case analysis, excluding individuals with missing covariates.

Proportional hazards assumption was assessed by testing the interactions between the exposures of interest and age at follow-up (the time scale of the analysis).

Secondary and Sensitivity Analyses—In secondary analyses, interaction terms were used to estimate separate hazard ratios for anticholinergic exposure categories according to several subgroups (sex, age at entry, and *APOE* genotype). We also performed several pre-specified sensitivity analyses designed to explore the possibility that an association between anticholinergic use and dementia could be attributed to anticholinergics used to treat early symptoms of dementia. First, we separated anticholinergic medications into two sub-types, antidepressants versus all other anticholinergic medication classes, and entered both sub-types into a single model. We hypothesized that if an association was strictly due to treatment of prodromal symptoms, a significant association with dementia would be found for antidepressants, but not for other anticholinergic medication classes. Next, we included the CES-D score category at each visit in the model rather than a history of depressive symptoms. Recent depression, rather than history of depression may be more strongly related to cognitive outcomes.[37] Finally, we extended the lag-time to two years and excluded the prescriptions during this period from the calculation of cumulative use. The longer lag-time decreases the likelihood that we included medications prescribed for prodromal symptoms. Post-hoc, we conducted an exploratory analysis to better understand our finding of increased dementia risk among those with the heaviest anticholinergic use by further defining heavy use sub-categories (primarily recent users, primarily past users or continuous users; eFigure 2).

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Table 1 provides participant characteristics overall and by 10-year cumulative exposure at study entry. The median age of participants at study entry was 74, 91% were white, 60% were female, and the majority had some college education. Overall, 78% had at least one fill for an anticholinergic medication in the 10 years prior to study entry (Table 1). Participants with anticholinergic use prior to study entry were more likely to be female, have fair or poor self-rated health, have higher depressive symptoms, and have comorbidities (e.g. hypertension, stroke, coronary heart disease, Parkinson's disease) than non-users. The most common anticholinergic drug classes used were antidepressants, antihistamines and bladder antimuscarinics (Table 2), which together accounted for over 90% of all anticholinergic exposure. The most common individual agents from these three drug classes were doxepin, chlorpheniramine and oxybutynin.

Over a mean (SD) follow-up of 7.3 (4.8) years, 797 (23%) participants developed dementia, of whom 637 (80%) were considered to have possible or probable AD. Table 3 shows unadjusted and adjusted risk estimates for dementia and AD associated with cumulative anticholinergic use. A 10-year cumulative dose-response relationship was observed for both dementia and Alzheimer's disease (test for trend, $p<0.001$). In particular, participants in the highest exposure category (>1095 days) had a statistically significant increased risk for dementia (adjusted HR 1.54, 1.21-1.96) or AD (HR 1.63; 1.24-2.14) compared to those with

no use. Participants in the next highest exposure level (366-1095 days) had a slightly elevated risk for dementia (HR 1.23; 0.94-1.62) and AD (HR 1.30; CI 0.96-1.76) compared with no use.

Our secondary analyses revealed no significant interactions with sex, age at entry, or *APOE* ε4 genotype and our exposure measure ($P > 0.05$). Moreover, our pre-specified sensitivity analyses supported the robustness of the main findings. Participants in the highest exposure category were at similarly elevated risk for dementia and AD compared to non-users (eTable 2), regardless of anticholinergic sub-type (antidepressant vs. other anticholinergic classes). Risk estimates also did not change appreciably when adjusting for recent rather than history of depressive symptoms (eTable 3), or extending the lag-time to 2 years (eTable 4). In our post-hoc analysis, we found that among those participants with the heaviest use (>1095 TSDD), that the timing of heavy use within the 10-year exposure window was not important; participants with cumulative exposure accrued primarily by past use had a similar increased risk for dementia as participants with continuous use or primarily recent use (eTable 5).

DISCUSSION

In this population-based, longitudinal study of persons age 65 years and older, we found that higher cumulative use of anticholinergic medications is associated with an increased risk for of all-cause dementia and Alzheimer's disease. Our findings were robust in secondary and sensitivity analyses, including those performed to take into account the potential use of anticholinergics (e.g., antidepressants) for prodromal symptoms of dementia. It is worth noting that the increased risk for dementia was consistent across anticholinergic subclasses, with increased risk found for people with high use of anticholinergic medications other than antidepressants, such as first generation antihistamines and bladder antimuscarinics. Thus our findings do not appear to be explained by protopathic bias due to treatment of depression, a condition commonly seen in patients with early undiagnosed dementia.

Our study findings are consistent with two cohort studies that have examined anticholinergic use and incident dementia risk.[1,14] In a large population based cohort study of individuals age 65 years and older living in France, chronic anticholinergic use was associated with an increased risk for dementia (adjusted HR 1.65) and AD (adjusted HR 1.94) over 4 years of follow-up.[14] Based on the exposure definition used in this study, it is difficult to determine the temporal relationship between chronic exposure and outcome, and protopathic bias cannot be ruled out. Another study conducted in Germany among primary care patients 75 years and older found that any anticholinergic use during the 54 month study period was associated with an increased risk for dementia (adjusted HR 2.0) compared to non-use.[1] Our results are not directly comparable to the German study because they also used a different exposure definition.

Our study has a number of strengths when compared to these previous studies. Specifically, using computerized pharmacy data to ascertain exposure in this cohort of older adults with long-term enrollment in their health plan, we were able to characterize medication use 10-years before study entry and throughout follow-up, to capture detailed cumulative

anticholinergic exposure. As described previously, other studies had limited ability to capture long-term cumulative exposure because of the method of exposure ascertainment.[1,14] In addition, we were able to examine whether risk varies according to extent of cumulative exposure and exclude use that may have been for prodromal symptoms. We were able to look separately at anticholinergic use by drug class, comparing effects of antidepressant medications to other classes. Additional strengths include the large community based sample, the average of over 7 years of follow-up, and the use of standard definitions for dementia and AD ascertainment.

We found that among the heaviest users, people who had past heavy use had a similar dementia risk as those with recent or continued heavy use. This suggests that the risk for dementia with anticholinergic use may persist despite discontinuation. Carriere et al. also reported an elevated dementia risk in people who had discontinued their anticholinergics, but the findings were not significant, likely because of lack of power.[14] Further study is needed to better understand whether dementia risk is attenuated after anticholinergic discontinuation as this has important clinical implications.

The mechanism by which anticholinergic medications might contribute to dementia risk has not been elucidated; however, a few lines of evidence suggest that it is biologically plausible. In a small autopsy study of patients with Parkinson's disease, participants that were receiving anticholinergic drugs for two years or longer had increased levels of AD neuropathology compared with those using for shorter durations.[15] Moreover, in animal models, reduced cholinergic transmission via atropine or cortical cholinergic denervation increased amyloid beta concentrations.[38-40]

A few potential limitations should be noted. Several methods exist for estimating anticholinergic burden, with no single gold standard.[41] We focused on high potency anticholinergics based on pharmacology and our list is in alignment with what is endorsed by the American Geriatrics Society.[8,41] Misclassification of exposure is possible because several first-generation antihistamines are available as over the counter (OTC) medications. However, GH members often purchase OTC medications at health plan pharmacies, and these purchases are recorded in the computerized pharmacy database, improving data capture. As in any observational study, unmeasured or residual confounding could introduce bias in our estimates. We did however control for a number of factors not typically found in studies restricted to administrative data (e.g., self-rated health, depressive symptoms). Our exposure measure relied on prescription fills and does not guarantee that the medication was consumed. Finally, the generalizability is unknown and our findings will need replication in other samples with greater numbers of minorities.

In conclusion, an increased risk for dementia was seen in people with higher use of anticholinergic medications. Our findings suggest that a person taking an anticholinergic medication such as oxybutynin 5 mg daily or doxepin 10 mg daily for more than 3 years would have a greater risk for dementia. Prescribers should be aware of this potential association when considering anticholinergic medications for their older patients and should consider alternatives when possible. For conditions where therapeutic alternatives may not be available, prescribers should use the lowest effective dose and discontinue therapy if

ineffective. These findings also have public health implications for education of older adults about potential safety risks since some anticholinergic medications are available as OTC products. Given the devastating consequences of dementia, informing older adults about this potential modifiable risk would allow them to choose alternative products and collaborate with their health professionals to minimize overall anticholinergic use. Further studies are needed to confirm these findings and to understand the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Participants at Study Entry, Overall and by Prior 10-Year Cumulative Anticholinergic Medication Use[a]

	All Subjects	Cumulative anticholinergic medication use in 10 years before study entry (TSDD)				
		None	1-90	91-365	366-1095	>1095
	N=3434	N=745	N=1083	N=701	N=347	N=558
Age in years, median (IQR)	74.4 (70, 80)	73.0 (69, 78)	74.7 (71, 80)	74.5 (70, 80)	75.1 (70, 80)	74.7 (70, 80)
Male	1387 (40.4)	384 (51.5)	474 (43.8)	271 (38.7)	116 (33.4)	142 (25.5)
White	3134 (91.4)	686 (92.1)	982 (90.8)	640 (91.7)	309 (89.1)	517 (92.8)
College education	2279 (66.4)	544 (73.0)	686 (63.3)	458 (65.4)	228 (65.7)	363 (65.1)
Obese	853 (25.4)	160 (21.9)	254 (23.8)	177 (25.8)	91 (26.8)	171 (32.0)
Current smoker	173 (5.1)	35 (4.7)	60 (5.6)	22 (3.2)	19 (5.5)	37 (6.6)
Regular exercise[b]	2453 (71.6)	563 (75.9)	801 (74.1)	498 (71.1)	235 (67.7)	356 (64.0)
Fair or poor self-reported health	532 (15.5)	65 (8.8)	136 (12.6)	127 (18.1)	66 (19.0)	138 (24.8)
Treated hypertension[c]	1662 (48.4)	292 (39.2)	501 (46.3)	367 (52.4)	177 (51.0)	325 (58.2)
Treated diabetes[d]	272 (7.9)	47 (6.3)	77 (7.1)	63 (9.0)	33 (9.5)	52 (9.3)
History of stroke	221 (6.4)	34 (4.6)	42 (3.9)	51 (7.3)	31 (8.9)	63 (11.3)
Coronary heart disease	633 (18.4)	94 (12.6)	205 (18.9)	135 (19.3)	87 (25.1)	112 (20.1)
Parkinson's disease	24 (0.7)	5 (0.7)	5 (0.5)	7 (1.0)	1 (0.3)	6 (1.1)
High depressive symptoms[e]	336 (10.0)	29 (4.0)	80 (7.5)	79 (11.4)	58 (16.8)	90 (16.5)
Current benzodiazepine use[f]	96 (2.8)	1 (0.1)	20 (1.9)	19 (2.7)	16 (4.6)	40 (7.2)
APOE ε4 genotype	768 (25.7)	163 (24.6)	234 (24.7)	159 (26.0)	89 (29.6)	123 (26.2)

TSDD Total Standardized Daily Dose; IQR, interquartile range

[a] Values are numbers (percentages) unless otherwise stated. Column percentages are based on non-missing data. Missing data is <1% for each covariate except for body mass index (2.2% overall), depressive symptoms (1.6% overall)

[b] ≥15min of activity at least three times a week

[c] Two or more fills in computerized pharmacy data for antihypertensive medications in the year prior to ACT enrollment

[d] One fill in computerized pharmacy data for an oral hypoglycemic medication or insulin in the year prior to ACT enrollment

[e] Modified version of the Center for Epidemiologic Studies Depression (CES-D) score of 10 or greater

[f] Two or more fills in computerized pharmacy data for a benzodiazepine in 6 months prior to ACT enrollment

Table 2

Any and Cumulative Anticholinergic Use During Study Period

	All participants (N=3434)		TSDD [a]	
Medication Class	**N[b]**	**%**	**Total TSDD filled**	**% of all TSDD**
Antihistamines	2,224	64.8	1,158,404	17.2
Gastrointestinal antispasmodics	1,566	45.6	365,141	5.4
Antivertigo/antiemetics	1,433	41.7	154,488	2.3
Antidepressants	1,352	39.4	4,241,590	63.1
Bladder antimuscarinics	668	19.5	702,825	10.5
Skeletal muscle relaxants	175	5.1	20,274	0.3
Antipsychotics	38	1.1	45,888	0.7
Antiarrhythmic	22	0.6	31,249	0.5
Antiparkinson agents	12	0.3	1,615	0.0
Total			6,721,473	100.0

TSDD Total Standardized Daily Dose

[a] A participant's study period included 10 years prior to study entry through the time they were diagnosed with dementia or censored. We summed TSDD for all participants for their entire study period.

[b] Number of participants with at least 1 fill for a medication in the category at any time during the follow-up period. Participants may have fills in multiple drug categories so the percentages do not sum to 100%.

Table 3

Association of Incident Dementia and Alzheimer's Disease with 10-year Cumulative Anticholinergic Medication Use[a]

			Unadjusted[c,d]		Adjusted[d,e]	
TSDD[b]	**Follow-up time (person-years)**	**Number of Events**	**HR**	**95% CI**	**HR**	**95% CI**
Dementia						
0	5618	136	1.00	Reference	1.00	Reference
1-90	7704	203	0.96	0.77-1.20	0.92	0.74-1.16
91-365	5051	172	1.31	1.04-1.65	1.19	0.94-1.51
366-1095	2626	102	1.39	1.07-1.82	1.23	0.94-1.62
>1095	4022	184	1.77	1.40-2.23	1.54	1.21-1.96
Alzheimer's Disease						
0	5618	112	1.00	Reference	1.00	Reference
1-90	7704	168	0.96	0.75-1.24	0.95	0.74-1.23
91-365	5051	128	1.21	0.93-1.58	1.15	0.88-1.51
366-1095	2626	83	1.38	1.03-1.85	1.30	0.96-1.76
>1095	4022	146	1.73	1.34-2.24	1.63	1.24-2.14

TSDD Total Standardized Daily Dose; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

[a] Observations with missing adjustment variables are excluded from the model (n=115; 3.3%).

[b] TSDD example; the minimum effective daily dose for oxybutynin is 5 mg daily (=1 TSDD); a person would fall into the following TSDD category if they were using 5 mg daily for 45 days (TSDD 1-90); 5 mg daily for 180 days (TSDD 91-365); 5 mg daily for 720 days (TSDD 366-1095); 5 mg daily for 4 years (TSDD>1095)

[c] Age adjustment via the time-axis.

[d] Test for trend *P* value <0.001 for an association between exposure categories and each outcome

[e] Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, education, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes, stroke, coronary heart disease, Parkinson's disease, history of depressive symptoms, and current benzodiazepine use.