Original Investigation

Cumulative Use of Strong Anticholinergics and Incident Dementia
A Prospective Cohort Study

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IMPORTANCE Many medications have anticholinergic effects. In general, anticholinergic-induced cognitive impairment is considered reversible on discontinuation of anticholinergic therapy. However, a few studies suggest that anticholinergics may be associated with an increased risk for dementia.

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

DESIGN, SETTING, AND PARTICIPANTS Prospective population-based cohort study using data from the Adult Changes in Thought study in Group Health, an integrated health care delivery system in Seattle, Washington. We included 3434 participants 65 years or older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses.

EXPOSURES Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses (TSDDs) 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 updated as participants were followed up over time.

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

RESULTS The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia (637 of these [79.9%] developed Alzheimer disease). A 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, $P < .001$). For dementia, adjusted hazard ratios for cumulative anticholinergic use compared with nonuse were 0.92 (95% CI, 0.74-1.16) for TSDDs of 1 to 90; 1.19 (95% CI, 0.94-1.51) for TSDDs of 91 to 365; 1.23 (95% CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95% CI, 1.21-1.96) for TSDDs greater than 1095. A similar pattern of results was noted for Alzheimer disease. Results were robust in secondary, sensitivity, and post hoc analyses.

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

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

The prevalence of anticholinergic use in older adults ranges from 8% to 37%.[1-5] This frequent use is despite the conclusions of professional organizations that the benefits of using these agents in older adults may be outweighed by the risks.[6-8] A well-known risk with anticholinergics is acute impairment in specific aspects of cognition (eg, working memory, attention, and 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 on discontinuation of medication therapy. However, several investigators[1,2,14] have reported that anticholinergics may be associated with an increased risk for sustained cognitive deficits, such as mild cognitive impairment or dementia. One biologically plausible mechanism for these findings is that cumulative use of these agents results in pathologic changes in the brain similar to those observed with Alzheimer disease (AD).[15] These observational studies have 4 important limitations. First, current anticholinergic use was ascertained at study entry and periodically during follow-up only by conducting a medication inventory.[1,14] Second, these studies lacked information about the dose and duration of anticholinergic use. Third, these studies had short follow-up periods. This last point is important because the pathophysiological changes in the brains of patients 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, 2 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 (eg, prodromal) symptoms of dementia. Given the potentially enormous public health implications, a better understanding of the possible risks of cumulative anticholinergic use is needed.

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

Methods

Design, Study Setting, and Participants

The research protocol for this population-based prospective cohort study was reviewed and approved by the institutional review boards of Group Health (GH) and the University of Washington, Seattle. Participants provided written informed consent.

Group Health is an integrated health care delivery system in the northwestern United States. Participants were from the Adult Changes in Thought (ACT) study, and details about study procedures have been detailed elsewhere.[20] Briefly, study participants 65 years or older were sampled randomly from Seattle-area GH members. Participants with dementia were excluded. The original cohort of 2581 participants was enrolled from 1994 through 1996. An additional 811 participants were enrolled from 2000 through 2003. In 2004, the study began continuous enrollment to replace those who died or dropped out. Participants underwent assessment at study entry and returned biennially to evaluate cognitive function and collect demographic characteristics, medical history, health behaviors, and health status. The present study sample was limited to participants with at least 10 years of GH health care plan enrollment before study entry to permit sufficient and equal ascertainment of cumulative anticholinergic exposure. The study sample was further limited to those with at least 1 follow-up study visit, which is necessary to detect incident dementia. Of the 4724 participants enrolled in the ACT study, 3434 were eligible for the present study (2 withdrew consent to use GH data for research, 674 had <10 years of GH enrollment, and 614 had no follow-up visits). Data through September 30, 2012, were included in these analyses.

Identification of Dementia and AD

We used the Cognitive Abilities Screening Instrument to screen for dementia at study entry and each biennial study visit.[21] The Cognitive Abilities Screening Instrument scores range from 0 to 100, with higher scores indicating better cognitive performance. Participants with scores of 85 or less (sensitivity, 96.5%; specificity, 92.0%)[22] underwent a standardized diagnostic evaluation for dementia, including a physical and neurologic 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 the 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 at which the diagnosis was made and the preceding visit. Participants with new-onset dementia underwent at least 1 annual follow-up examination to confirm the diagnosis of dementia.

Anticholinergic Use

Medication use was ascertained from the GH computerized pharmacy dispensing data that included the name, strength, route of administration, date dispensed, and amount dis-

pensed for each drug. *Anticholinergics* were defined as those medications deemed to have strong anticholinergic activity as per consensus by an expert panel of health care professionals.[8] Because we drew on medication data from as early as 1984 (eg, extending back 10 years before study entry), this contemporary list was enhanced with medications no longer on the market. Therefore, 2 clinician investigators (S.L.G. and J.T.H.) reviewed previously published standard pharmacology/pharmacotherapy reference books to identify additional anticholinergics.[25,26] eTable 1 in the Supplement lists the strong anticholinergics according to medication class (eg, first-generation antihistamines, tertiary tricyclic antidepressants, and 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. We then calculated a standardized daily dose (SDD) by dividing the product by the minimum effective dose per day recommended for use in older adults according to a well-respected geriatric pharmacy reference (eTable 1 in the Supplement).[27] For each participant, we summed the SDD for all anticholinergic pharmacy fills during the exposure period to create a cumulative total SDD (TSDD) (an example calculation appears in eFigure 1 in the Supplement). This previously published method allows for standardized conversion of doses of different anticholinergics into a single exposure measure so that we are able to capture overall anticholinergic burden.[28,29]

The primary measure of anticholinergic use was the 10-year cumulative exposure (eFigure 2 in the Supplement). Prescription fills in the most recent 1-year period were excluded because of concern about protopathic bias.[30] Our exposure varied over time; we assessed 10-year cumulative exposure at study entry and updated the exposure as participants were followed up over time. We categorized cumulative exposure (TDSS) as no use, 1 to 90, 91 to 365, 366 to 1095, or greater than 1095 (ie, >3 years), with cut points based on clinical interpretability and the exposure distribution observed in our sample. As an example, individuals would reach the heaviest level of exposure if they took any of the following medications daily for more than 3 years: oxybutynin chloride, 5 mg; chlorpheniramine maleate, 4 mg; olanzapine, 2.5 mg; meclizine hydrochloride, 25 mg; or doxepin hydrochloride, 10 mg.

Covariates

Based on a review of the literature, we selected covariates that may confound the relationship between anticholinergic use and dementia.[13,14] Information about covariates came from standardized questionnaires that were administered by research staff at each study visit or from GH electronic health databases. Demographic factors included age, sex, and years of education (at least some college vs none). Body mass index was calculated as the weight in kilograms divided by the height in meters squared (ie, underweight, <18.5; normal weight, 18.5-24.9; overweight, 25.0-29.9; and obese, ≥30.0).[31] Participants were asked about current smoking status and whether they engaged in regular exercise (self-report of performing 1 of several listed activities for ≥15 minutes, ≥3 times per week).[32] We created dichotomous variables for self-rated health status (fair/poor vs better) and specific comorbidities, including medication-treated hypertension and diabetes mellitus (computerized pharmacy data), history of stroke (ie, self-report or codes 430.X, 431.X, 432.X, 434.X, 436.X, and 438.X from the *International Classification of Diseases, Ninth Revision*), and coronary heart disease (ie, self-reported history of heart attack, angina, angioplasty, or coronary artery bypass surgery). Apolipoprotein E (*APOE*) allele 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 owing to confounding by indications such as self-reported history of Parkinson disease, high levels of depressive symptoms (ie, score of ≥10 on the short version of the Center for Epidemiologic Studies Depression Scale),[35] and current benzodiazepine use (computerized pharmacy data) as a proxy for sleep or anxiety disorders.

Statistical Analysis

We used multivariable Cox proportional hazards regression models, with the participant's age as the time scale[36] to estimate hazard ratios (HRs) and 95% CIs for the association between anticholinergic use and incident dementia or possible/probable AD. Participants were censored at the earlier of their last ACT visit, disenrollment from the GH health care plan, or death if they did not have a diagnosis of dementia. In addition, for the AD analysis, individuals were censored at the time of the diagnosis of dementia 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 interaction between the exposure and age at follow-up (the time scale of the analysis).

In secondary analyses, interaction terms were used to estimate separate HRs for anticholinergic exposure categories according to several subgroups (sex, age at entry, and *APOE* genotype). We also performed several prespecified 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 anticholinergics into antidepressants vs all other anticholinergic classes and entered both subtypes into a single model. We hypothesized that if an association strictly was due to treatment of prodromal symptoms, a significant association with dementia would be found for antidepressants but not for other anticholinergic classes. Next, we included the Center for Epidemiologic Studies Depression Scale score category at each visit in the model rather than a history of depressive symptoms. Recent depression rather than a history of depression may be more strongly related to cognitive outcomes.[37] Finally, we extended the lag time to 2 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. We conducted a post hoc ex-

Table 1. Characteristics of Participants at Study Entry

Characteristic	All (N = 3434)	Participant Group[a]				
		Cumulative Anticholinergic Medication Use in 10 y Before Study Entry, TSDD[b]				
		None (n = 745)	1-90 (n = 1083)	91-365 (n = 701)	366-1095 (n = 347)	>1095 (n = 558)
Age, median (IQR), y	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 sex	1387 (40.4)	384 (51.5)	474 (43.8)	271 (38.7)	116 (33.4)	142 (25.5)
White race	3134 (91.4)	686 (92.1)	982 (90.8)	640 (91.7)	309 (89.1)	517 (92.8)
College education (n = 3433)	2279 (66.4)	544 (73.0)	686 (63.3)	458 (65.4)	228 (65.7)	363 (65.1)
Obese (n = 3359)	853 (25.4)	160 (21.9)	254 (23.8)	177 (25.8)	91 (26.8)	171 (32.0)
Current smoker (n = 3427)	173 (5.0)	35 (4.7)	60 (5.6)	22 (3.2)	19 (5.5)	37 (6.6)
Regular exercise (n = 3426)[c]	2453 (71.6)	563 (75.9)	801 (74.1)	498 (71.1)	235 (67.7)	356 (64.0)
Fair or poor self-reported health (n = 3429)	532 (15.5)	65 (8.8)	136 (12.6)	127 (18.1)	66 (19.0)	138 (24.8)
Treated hypertension (n = 3404)[d]	1662 (48.8)	292 (39.2)	501 (46.3)	367 (52.4)	177 (51.0)	325 (58.2)
Treated diabetes mellitus[e]	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 disease (n = 3427)	24 (0.7)	5 (0.7)	5 (0.5)	7 (1.0)	1 (0.3)	6 (1.1)
High level of depressive symptoms (n = 3378)[f]	336 (9.9)	29 (4.0)	80 (7.5)	79 (11.4)	58 (16.8)	90 (16.5)
Current benzodiazepine use[g]	96 (2.8)	1 (0.1)	20 (1.9)	19 (2.7)	16 (4.6)	40 (7.2)
APOE ε4 genotype (n = 2991)	768 (25.7)	163 (24.6)	234 (24.7)	159 (26.0)	89 (29.6)	123 (26.2)

Abbreviations: *APOE*, apolipoprotein E; IQR, interquartile range; TSDD, total standardized daily dose.

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants. Column percentages are based on nonmissing data. Sample size is given in column 1 for variables with missing values. *APOE* ε4 genotype was not entered into primary models.

[b] Calculated by multiplying tablet strength by the number of tablets dispensed and dividing the product by the minimum effective dose per day recommended for use in older adults according to a well-respected geriatric pharmacy reference (SDD). We then summed the SDDs for all anticholinergic pharmacy fills during the exposure period for each participant.

[c] Indicates at least 15 minutes of activity at least 3 times per week.

[d] Indicates 2 or more fills in computerized pharmacy data for antihypertensives in the year before enrollment in the Adult Changes in Thought (ACT) study.

[e] Indicates 1 fill in computerized pharmacy data for an oral hypoglycemic medication or insulin in the year before enrollment in the ACT study.

[f] Indicates a score of 10 or greater on the modified version of the Center for Epidemiologic Studies Depression Scale.

[g] Indicates 2 or more fills in computerized pharmacy data for a benzodiazepine in the 6 months before enrollment in the ACT study.

ploratory analysis to understand better our finding of increased dementia risk among those with the heaviest anticholinergic use by further defining heavy use subcategories (primarily recent users, primarily past users, or continuous users) (eFigure 2 in the Supplement). All analyses were performed using commercially available statistical software (SAS, version 9.2; SAS Institute Inc).

Results

Table 1 provides participant characteristics overall and by 10-year cumulative exposure at study entry. The median age of the participants at study entry was 74.4 years; 91.4% were white, 59.6% were women, and most (66.4%) had some college education. Overall, 78.3% had at least 1 fill for an anticholinergic in the 10 years before study entry (Table 1). Participants with anticholinergic use before study entry were more likely to be women, to have fair or poor self-rated health, to have higher levels of depressive symptoms, and to have comorbidities (eg, hypertension, stroke, coronary heart disease, or Parkinson disease) than nonusers. The most common anticholinergic classes used were antidepressants, antihistamines, and bladder antimuscarinics (**Table 2**), which together accounted for more than 90% of all anticholinergic exposure. The most common individual agents from these 3 drug classes were doxepin, chlorpheniramine, and oxybutynin.

During a mean (SD) follow-up of 7.3 (4.8) years, 797 participants (23.2%) developed dementia, of whom 637 (79.9%) 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 dementia and AD (test for trend, $P < .001$). In particular, participants in the highest exposure category (TSDD >1095) had a statistically significant increased risk for dementia (adjusted HR, 1.54 [95% CI, 1.21-1.96]) or AD (adjusted HR, 1.63 [95% CI, 1.24-2.14]) compared with those with no use. Participants in the next highest exposure level (TSDD, 366-1095) had a slightly elevated risk for dementia (adjusted HR, 1.23 [95% CI, 0.94-1.62]) and AD (adjusted HR, 1.30 [95% 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 ($P > .05$ for all comparisons). Moreover, our prespecified 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 with nonusers (eTable 2 in the Supplement) regardless of anticholinergic subtype (antidepressant

vs other anticholinergic classes). Risk estimates also did not change appreciably when adjusting for recent rather than a history of depressive symptoms (eTable 3 in the Supplement) or when extending the lag time to 2 years (eTable 4 in the Supplement). In our post hoc analysis, we found that, among those participants with the heaviest use (TSDD, >1095), the timing of heavy use within the 10-year exposure window was not important; participants with cumulative exposure accrued primarily by past use had an increased risk for dementia similar to that of participants with continuous use or primarily recent use (eTable 5 in the Supplement).

Discussion

In this population-based, longitudinal study of persons 65 years or older, we found that higher cumulative use of anticholinergics is associated with an increased risk for all-cause dementia and AD. Our findings were robust in secondary and sensitivity analyses, including those performed to take into account the potential use of anticholinergics (eg, antidepressants) for prodromal symptoms of dementia. The increased risk for dementia that remained consistent across anticholinergic subclasses is worth noting, with an increased risk found for people with high use of anticholinergics 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 2 cohort studies that have examined anticholinergic use and incident dementia risk.[1,14] In a large population-based cohort study of individuals 65 years or older living in France,[14] long-term anticholinergic use was associated with an increased risk for dementia (adjusted HR, 1.65) and AD (adjusted HR, 1.94) during 4 years of follow-up. Based on the exposure definition used in that study, determining the temporal relationship between long-term exposure and outcome is difficult, and protopathic bias

Table 2. Any and Cumulative Anticholinergic Use During the Study Period

Medication Class	All Participants, No. (%) (N = 3434)[a]	Total TSDDs Filled (% of All TSDDs)[b]
Antihistamines	2224 (64.8)	1 158 404 (17.2)
Gastrointestinal tract antispasmodics	1566 (45.6)	365 141 (5.4)
Antivertigo agents/antiemetics	1433 (41.7)	154 488 (2.3)
Antidepressants	1352 (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)
Antiarrhythmics	22 (0.6)	31 249 (0.5)
Antiparkinsonians	12 (0.3)	1615 (0.02)
Total		**6 721 473** (100)

Abbreviation: TSDD, total standardized daily dose.

[a] Indicates the 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 total 100%.

[b] Calculation of the TSDD is described in Table 1. A participant's study period included the 10 years before study entry through the time they were diagnosed as having dementia or censored. We summed the TSDDs for all participants for their entire study period. We have rounded numbers for individual medication classes.

Table 3. Association of Incident Dementia and AD With 10-Year Cumulative Anticholinergic Use[a]

Diagnosis, TSDD[b]	Follow-up Time, Person-years	No. of Events	HR (95% CI)	
			Unadjusted[c,d]	Adjusted[d,e]
Dementia				
0	5618	136	1 [Reference]	1 [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)
AD				
0	5618	112	1 [Reference]	1 [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)

Abbreviations: AD, Alzheimer disease; HR, hazard ratio; TSDD, total standardized daily dose.

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

[b] Calculation of the TSDD is described in Table 1.

[c] Adjusted for age via the time axis.

[d] $P < .001$, test for trend, for an association between exposure categories and each outcome.

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

cannot be ruled out. Another study conducted in Germany among primary care patients 75 years or older[1] found that any anticholinergic use during the 54-month study period was associated with an increased risk for dementia (adjusted HR, 2.08) compared with nonuse. Our results are not directly comparable to those of the German study because they also used a different exposure definition.

Our study has a number of strengths when compared with these previous studies. We used computerized pharmacy data to ascertain exposure in this cohort of older adults with long-term enrollment in their health care plan and were able to characterize medication use 10 years before study entry and throughout follow-up; this process captured detailed cumulative anticholinergic exposure. As described previously,[1,14] other studies had limited ability to capture long-term cumulative exposure because of the method of exposure ascertainment. In addition, we were able to examine whether risk varies according to the extent of cumulative exposure and to exclude use that may have been for prodromal symptoms. We were able to look separately at anticholinergic use by drug class, comparing the effects of antidepressants with those of other classes. Additional strengths include the large community-based sample, the mean follow-up of more than 7 years, and the use of standard definitions for dementia and AD ascertainment.

We found that, among those with the greatest TSDDs, participants with primarily past use had a dementia risk similar to those with greater recent or continuous use. This finding suggests that the risk for dementia with anticholinergic use may persist despite discontinuation of therapy. Carrière et al[14] also reported an elevated dementia risk in people who had discontinued their anticholinergic therapy, but the findings were not significant, likely because of a lack of power. Additional studies are needed to better understand whether dementia risk is attenuated after discontinuation of anticholinergic therapy, which has important clinical implications.

The mechanism by which anticholinergics might contribute to dementia risk has not been elucidated; however, a few lines of evidence suggest biological plausibility. In a small autopsy study of patients with Parkinson disease,[15] participants who used anticholinergics for 2 years or longer had increased levels of AD neuropathologic features compared with those who used anticholinergics for shorter durations. Moreover, in animal models, reduced cholinergic transmission via atropine or cortical cholinergic denervation increased β-amyloid concentrations.[38-40]

We should note a few potential limitations of our study. Several methods exist for estimating anticholinergic burden, with no single criterion standard.[41] We focused on high-potency anticholinergics based on pharmacologic properties, 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 medications. However, GH members often purchase over-the-counter medications at health care 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. However, we controlled for a number of factors not typically found in studies restricted to administrative data (eg, self-rated health, depressive symptoms). Our exposure measure relied on prescription fills and did 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 minority participants.

Conclusions

An increased risk for dementia was seen in people with higher use of anticholinergics. Our findings suggest that a person taking an anticholinergic, such as oxybutynin chloride, 5 mg/d, or doxepin hydrochloride, 10 mg/d, for more than 3 years would have a greater risk for dementia. Prescribers should be aware of this potential association when considering anticholinergics for their older patients and should consider alternatives when possible. For conditions with no therapeutic alternatives, prescribers should use the lowest effective dose and discontinue therapy if ineffective. These findings also have public health implications for the education of older adults about potential safety risks because some anticholinergics are available as over-the-counter products. Given the devastating consequences of dementia, informing older adults about this potentially modifiable risk would allow them to choose alternative products and collaborate with their health care professionals to minimize overall anticholinergic use. Additional studies are needed to confirm these findings and to understand the underlying mechanisms.

ARTICLE INFORMATION

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Study concept and design: Gray, Anderson, Dublin, Hanlon, Walker.
Acquisition, analysis, or interpretation of data: Gray, Anderson, Dublin, Hubbard, Walker, Yu, Crane, Larson.
Drafting of the manuscript: Gray, Anderson, Hanlon.
Critical revision of the manuscript for important intellectual content: Gray, Anderson, Dublin, Hubbard, Walker, Yu, Crane, Larson.
Statistical analysis: Anderson, Hubbard, Walker.
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Study supervision: Gray.

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