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Anticholinergic Drug Use and Risk of Cognitive Performance in Older Adults with Questionable Cognitive Impairment: A Cross-Sectional Analysis

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Abstract

Background—Age-associated decline in central cholinergic activity makes older adults susceptible to harmful effects of anticholinergic (AC) medications. However, there is an inadequate understanding of association and possible effects of AC drugs on cognition. This cross-sectional study examines the associations of AC medications on cognition among older adults with questionable cognitive impairment (QCI).

Methods—For this cross-sectional study, we used multicenter database of community dwelling older adults (N=7,351) aged 60+ years with QCI from September 2005 until March 2014 as baseline data. Anticholinergic Drug Scale was used to categorize AC drug load in no, low or moderate/high groups. Individuals with clinical dementia rating-sum of boxes score between 0.5 and 2.5 were identify as having QCI. Cognitive performance was evaluated using Neuropsychological Test Battery. The mean z-scores of neuropsychological tests were grouped into a global cognition score.

Results—Participants who took AC medications were older, largely female and had higher prevalence of incontinence than those without AC exposure. Global cognition was significantly greater in moderate/high AC group than no AC group (-0.23 ± 0.53 vs. -0.32 ± 0.53). Multivariable linear regression showed that global cognition score among low and moderate/high AC groups, as compared to no AC group, was higher by 0.064 ($P=.006$ and $P=.12$, respectively).

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interests Sunil Swami, Ronald Cohen, John Kairalla and Todd Manini declare that there is no potential conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, this is a retrospective study and the formal consent is not required.

Conclusions—This cross-sectional study indicates that older adults with QCI who were exposed to AC medications might have higher global cognitive scores than those without AC exposure. The observed associations indicate that older adults might experience some beneficial cognitive effects from AC drugs, possibly due to the therapeutic effects of these medications in controlling comorbidities; thus, outweighing their adverse effects on cognition.

1 Introduction

About 5.3 million people [1] in the U.S. suffer from Alzheimer's disease (AD) and with the increasing older population the incidence of AD is expected to triple over the next 40 years [2]. Notably, 60–80% of the overall dementia cases are identified as dementia of Alzheimer's type. AD is characterized by cortical cholinergic deficits, cognitive impairment, and dementia [3]. The cholinergic deficit was once considered the key pathophysiological dysfunction causing dementia, which led to the cholinergic hypothesis of AD [4]. Various studies have established that cholinergic neuronal loss, acetylcholine receptor dysfunctions, and signaling dysregulation are associated with decline in learning and memory in AD [5, 6]; and the severity of dementia is directly correlated with atrophy and degeneration of the brain cholinergic pathways [7, 8]. However, less is known about whether the exogenous use of anti-cholinergic (AC) medications is connected to age-related cognitive impairment.

Previous studies have shown that older adults with exposure to AC medications were at increased risk of adverse drug events [9, 10]; especially related to decline in cognitive [11–13] and physical abilities [14]. Although there has been considerable attention directed at monitoring and minimizing AC drug load to minimize cognitive impairment, these medications with moderate/high AC properties like Oxybutynin for urinary incontinence and Carbamazepine for neuropathic pain are frequently prescribed, and medications like Diphenhydramine (Trade name: Benadryl) are readily available over-the-counter as a general antihistaminic [15]. Despite these clinical benefits, there are clear biological adverse effects on cognition [16] through unselective antagonism of muscarinic receptors in the brain [17]. Unfortunately, older adults are more susceptible to central anti-muscarinic adverse effects [18] making them more vulnerable to the adverse effects of AC drugs.

Current understanding of the effects of AC drugs on human cognition is derived largely from the studies that compare AC medication effects on individuals with mild cognitive impairment (MCI) or dementia to individuals with normal cognition [20–22]. Previous observational studies have reported that moderate/high AC burden is associated with greater risk of cognitive impairment and long-term cognitive decline in older adults [11–13, 23–25]. However, the pathophysiological process of AD and associated dementia begins years before the emergence of clinically detectable signs and symptoms [19]; and thus provide a window of opportunity to identify individuals with minimal cognitive impairment, and intervene and delay the process of cognitive decline in the very early stage of dementia. Clinical Dementia Rating-Sum of Boxes Score (CDR-SOB) is a tool to assess and classify levels of cognitive impairment in various categories; and its questionable cognitive impairment (QCI) category identifies individuals between the normal cognition and the mild cognitive impairment (MCI). On the path of dementia development, QCI is the first stage of cognitive impairment between normal cognition and full blown dementia. QCI is the neuropsychological profile of

a patient in the very early stage of cognitive impairment which does not manifest clinical signs or symptoms of cognitive decline but can be revealed on neuropsychological assessments. When QCI worsens, patients move from QCI into to MCI stage [26, 27]. Therefore, QCI provides the opportunity to identify a select number of people who might be vulnerable to the effects of AC medications and have elevated risk of clinical onset of MCI and dementia. Understanding the effects of AC medications in these vulnerable group will not only provide greater insight into the role of AC medications on cognition but also help in planning strategies to delay cognitive decline in this group. However, there is a major gap in understanding the role of AC exposure in older adults with QCI. Therefore, the objective of the proposed study is to assess the associations of AC medication exposure on cognitive performance among older adults with QCI. We hypothesize that older adults with QCI who have exposure to AC drugs are more likely to have poor cognitive scores as compared to older adults who have no exposure to AC drugs.

2 Methods

2.1 Study Participants

This study is a part of larger multi-center longitudinal cohort database— National Alzheimer's Coordinating Center (NACC)—that includes community dwelling older adults with normal cognition, MCI, dementia, and AD [28]. The NACC contains a comprehensive database, the Uniform Data Set (UDS) from 34 collaborating Alzheimer's Disease Centers (ADCs) [29]. The sample for this study consists of individuals from the NACC UDS data who participated in the study from September 2005 until March 2014 and were selected from the hospital, patient, and physician referrals. Individuals aged 60 and above were enrolled in the study (in 2005), and their baseline anticholinergic exposure and cognitive functions were evaluated at the time of enrollment. QCI was determined by the reliable and valid instrument—Washington University Clinical Dementia Rating-Sum of Boxes (CDR-SOB) scale [30]. The CDR-SOB score is a detailed quantitative rating scale with a wide range of values (0–18) identifying various stages of cognitive impairment differentiating between QCI and mild cognitive impairment. For our analysis, QCI was defined as CDR-SOB score between 0.5–2.5 [31].

2.2 Anticholinergic Exposure

To assess AC drug exposure, we used the valid and reliable Anticholinergic Drug Scale (ADS) — an ordinal drug scale that rates medications according to increasing potency of their AC activity [32]. ADS include 413 medications covering about 88 and 89 percent of regular and as-needed drugs, respectively. A clinician or a trained research staff recorded each participant's prescription drugs, non-prescription medications and vitamins/supplements using a standard medication inventory. The medication list included various medication groups like antivirals, antibiotics, antidepressants, antihistaminics, antipsychotics, antianxiety, analgesics, cardiovascular drugs, muscle relaxants, H2 antagonists, corticosteroids, anticonvulsants etc. ADS scores are divided into four levels (0, 1, 2, and 3) according to AC drug activity [32]. ADS level 0 includes drugs with no known anticholinergic properties, ADS level 1 includes drugs in which anticholinergic activities can be assessed by receptor binding study, ADS level 2 includes drugs that shows anticholinergic

adverse events at excessive doses, and ADS level 3 includes drugs that have marked anticholinergic properties. ADS also includes prescription medications like galantamine, rivastigmine, donepezil, and memantine approved by Food and Drug Administration to treat individuals diagnosed with AD as these medications do not have anticholinergic properties and are therefore included in ADS level 0. For the purpose of our study; we categorized the ADS drugs into three levels—Level 1 indicates drugs with no known AC properties (e.g. cetirizine); Level 2 indicates drugs with low potential AC activity (e.g. diazepam); and Level 3 was created by combining ADS level 2 (e.g. ranitidine) and 3 (e.g. oxybutynin), which represent medications that have moderate/high AC adverse effects. The cognitive harm done by drugs of ADS level 2 and 3 are deleterious enough to manifest clinically significant cognitive impairment, which can be identified on clinical assessments. Therefore, based upon clinical significance of medications in ADS group 2 and 3, we decided to combine both categories into one single category, Level 3, in this study.

The NACC assessed participants' medication use of prescription, non-prescription, over-the-counter medications and supplements taken within two weeks prior to their baseline and follow up visits. The NACC recorded drugs from various medication groups such as antibiotics, antidepressants, antihistaminic, antipsychotics, antianxiety, cardiovascular drugs, H2 antagonists, anticonvulsants.

2.3 Cognitive Outcomes

We used NACC's standardized Neuropsychological Test Battery (NTB) to assess cognitive functions in the early stage of cognitive impairment [33]. The NTB can predict progression from QCI to dementia and demonstrate age-related changes in cognitive domains. The NACC NTB assessed attention by Digit Span Forward and Digit Span Backward from the Wechsler Memory Scale-Revised (WMS-R). Decline in episodic memory, a hallmark of early AD, was evaluated by Logic Memory, IA and delayed recall by Logic Memory, IIA. Executive functions were assessed using Trail Making Part A (TM-A) and B (TM-B) tests and digit symbol substitution test (DSST). Language (verbal fluency and naming) was assessed by Animal and Vegetable list generation test and a short version of the Boston Naming Test (BNT), respectively. Hayden et al. performed exploratory and confirmatory factor analysis of the NACC UDS NTB and grouped 12 NTB measures in four cognitive domains [34]. We used Hayden's factor structures approach and grouped cognitive measures in four cognitive domains—Memory, Attention, Executive, and Language. These domain specific cognitive measures were our secondary outcome. The domain scores were calculated as the mean z-scores of relevant cognitive tests. Global cognition score, the primary outcome, was calculated as an average of the four domain scores (Online Resource 1). Since the lower TM-A and TM-B scores indicate better executive functions, we reversed the sign of z-scores of TM-A and TM-B and added to the z-score of DSST to assess the executive functions in a common direction, i.e., higher scores indicate better cognitive functions.

The conceptual framework and the current literature guided the selection of independent variables. Previous studies have demonstrated association between dementia and demographic factors, lifestyle behaviors, clinical conditions, and genetic biomarkers [23–

25]. The demographic characteristics included age, sex, race, education, marital status, living situation, and family history. The lifestyle factors that affect cognition were smoking, alcohol consumption, and body mass index. Clinical conditions included comorbidities like cardiovascular disease, cerebrovascular disease, depression, neurological diseases and diabetes. Cardiovascular disease consisted of cardiac arrest, atrial fibrillation, congestive heart failure, and patients with procedure like angioplasty, cardiac bypass surgery and pacemaker implant. Cerebrovascular disease included patient of stroke and transient ischemic attack. Neurological disease involved seizures, traumatic brain injury and other neurological deficits. Diabetes, vitamin B12 deficiency, thyroid disease, and incontinence was identified by medical and prescription records and by subject or co-participant report. Depression was identified using Geriatric Depression Scale and self-report at the time of enrollment. We also controlled for gene ApoE4, a well-known genetic risk factor for AD and cognitive impairment [22].

2.4 Statistical Analysis

We performed descriptive analysis to evaluate distribution of means and proportions of baseline characteristics like demographics, lifestyle factors, clinical conditions, and genetic predisposition stratified by levels of anticholinergic burden (no, low, and moderate/high AC use). We performed analysis of variance to evaluate differences in the means of continuous variables; and chi-squared test to evaluate differences in the distribution of categorical variables. Descriptive statistics allowed us to quantify and compare the distribution of different cognitive measures among AC drug levels.

In this cross-sectional analysis, the potential association between lower cognitive scores on global cognition and cognitive domains among individuals taking AC drugs was examined using general linear models (GLM). To evaluate the primary outcome, GLM was fitted to estimate the independent association of AC drug exposures on global cognition score at baseline according to ADS levels. In addition, to assess effects of AC drug use on specific cognitive domains, we built domain-specific models to evaluate the independent association between AC drug exposure and cognitive domains of memory, attention, executive functions and language. We checked the linear model assumptions of independence, normality, and equal variance. We checked the independence by plotting each residual against neighboring value, i.e., residual lag plot. We illustrated the normal probability plot to observe against normal distribution values. Furthermore, we checked for the assumption of equal variance through residual plot examination. Statistical significance level was set at $\alpha=0.05$. Analysis was performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

3 Results

A total of 7,315 participants met the inclusion criteria at baseline (2005). The mean (m) age $\pm$ standard deviation (sd) of the sample was 74.8 ± 7.9 years (range: 60–109 years), 81.6% were white, and 51.8% were females. About 91% had high school or higher education, which appears to be high. However, there is similarity between the education levels of our cohorts QCI and other cohorts of preclinical AD [33, 35, 36]. Thus, our results can be generalized to this specific group of older population. Around 63.5% were married and

76.5% were living independently. About 15.7% and 4.1% participants were taking low and high levels of AC medication, respectively.

Table 1 shows the population characteristics across no, low, and moderate/high AC medication groups at baseline (2005). As compared to those who did not take AC medications, individuals who took low or moderate/high AC medications were slightly older (74.5 ± 7.8 vs. 76.6 ± 8.2 vs. 75.6 ± 7.8 , $P = <.001$), had higher BMI (27.1 ± 5.05 vs. 27.5 ± 5.5 vs. 27.4 ± 5.7 , $P = 0.02$), were less likely to be married (65% vs. 60% vs. 57%, $P = <.001$), more likely to live alone (27% vs. 31% vs. 33%, $P = <.001$), and less likely to live independent (77% vs. 74% vs. 75% , $P = .01$). The most commonly used AC medications with no AC properties were Aspirin (48%), Multivitamin (38%) and Donepezil (27%). Most commonly medications with low AC properties were Furosemide (9%), Warfarin (8%), and Sertraline (7%). Among the medications that had moderate/high AC properties, Ranitidine (4%), Oxybutynin (4%), and Alprazolam (3%) were the commonly used drugs (Online Resource 2).

The mean scores (Table 2) were significantly greater in moderate/high and low AC medication group as compared to no AC medication group for global cognition (-0.23 ± 0.53 vs. -0.24 ± 0.52 vs. -0.32 ± 0.53 ; $P = <.001$); and among cognitive domains of memory (-0.63 ± 1.18 vs. -0.68 ± 1.17 vs. -0.80 ± 1.15 ; $P = <.001$), attention (-0.33 ± 0.89 vs. -0.36 ± 0.85 vs. -0.40 ± 0.88 ; $P = .04$), executive function (0.56 ± 0.91 vs. 0.58 ± 0.91 vs. 0.48 ± 0.80 ; $P = <.001$), and language (-0.54 ± 0.97 vs. -0.53 ± 0.93 vs. -0.58 ± 0.97 ; $P = .08$). In the multivariable model (Table 3), controlling for baseline demographics, lifestyle, comorbidity, and genetic factors, the global cognition score was estimated to be 0.064 greater for low AC medication group than no AC medication group ($P = .006$). The global cognition score among moderate/high AC medication group was also estimated to be higher by 0.064 as compared to no AC medication group, but was not statistically significant ($P = .12$). The fully adjusted model explained about 15% of the variation in the model ($R^2 = 0.15$). Similarly, the cognitive scores among moderate/high AC medication group in the attention domain and low AC medication group in the language domain were higher by .214 ($P = .004$) and .090 ($P = .03$), respectively, as compared to those who did not take any AC medication.

4 Discussion

To our knowledge, this is the first population-based study to determine the association between AC medication use and cognitive functions in older adults with questionable cognitive impairment based upon their CDR-SOB score. The objective of this study was to assess the associations and possible effects of AC medication use on cognitive functions among older adults with QCI. We hypothesized that older adults with QCI who have exposure to AC drugs are more likely to have poor cognitive scores as compared to older adults who have no exposure to AC drugs. Our study results showed that older adults with QCI who took AC medication had higher cognitive score as compared to those who did not take AC medications. These associations were statistically significant for those who took low AC medication but were not significant for those who took moderate/high AC medication. Moreover, these associations were independent of demographic factors, clinical conditions, and APOE biomarker that might influence the cognition. Besides, older adults

with QCI who took moderate/high AC medications had greater score in attention domain and those who took low AC medications had greater score in language domain compared to those who did not take AC medication. Furthermore, a higher global cognition score of .064 indicates that the overall cognitive functions among individuals who took low and moderate/high AC medication were greater than for those not taking AC medications by a small, but significant margin measured over 10 cognitive tests (Online Resource 1), with consistent results across the cognitive domains (Table 2). This clinically significant finding is notable as previous studies have showed overall decrease in cognitive scores due to AC exposure. In pharmacoepidemiological research, prevalent user bias can seriously impact the inference. In this study, the medications were prescribed to the patients for various clinical conditions not directly related to the cognitive performance. Furthermore, it is possible that AC medications might influence the risk factors in the causal pathway that regulate cognitive performance. However, if AC medications would have had influenced covariates, it would have had reduced the cognitive performance, as shown in previous studies [37]. However, in this study we found that AC use was associated with higher cognitive score. This highlights that the prevalent user bias could be ruled out in this study. In case of a potential prevalent user bias in observational study, new-user designs can be implemented like, excluding prevalent users from the study, selecting comparative cohorts of equal exposure and follow-up periods, performing analysis from the start of the of the medication therapy, and including all early events in the analysis.

In our study, we found that the cognitive scores were significantly higher among individuals using AC medications as compared to those who did not use AC medications. In contrast with others, we found that there was no dose-response association between increased AC medication use and decreased cognition in QCI population [16, 33, 34]. These findings differ from the findings of previous population-based studies that used the list based method to assess AC medication load among cognitively healthy older adults or demented populations [12, 13, 40, 41]. However, our findings are compatible with a previous study that found non-demented patients were significantly less susceptible to the adverse cognitive effects of AC medication than those with AD [42], indicating that the older adults with QCI, compared to MCI or preexisting dementia, might be less susceptible to adverse effects of AC medications. One recent longitudinal study showed that AC medications use did not deteriorate cognition over a period of 18 months [34]. Therefore, our study results point to a specific population that may possibly benefit from AC medication use; however, further studies are needed to replicate and clarify a causal relationship for our findings. In this study, we found that women, as compared to men, took more medication with moderate/high AC properties. This might be attributed to greater longevity and potential age associated comorbidities among women [43]. Furthermore, prevalence of incontinence is higher among women; and one of the most commonly prescribed medication to treat incontinence is oxybutynin, which has a very high anticholinergic potency [44]. Similarly, greater proportion of patients with Parkinson's disease took medications with moderate/high AC properties like Bromocriptine. Therefore, it is important for clinicians to identify patients who might be at a greater risk of AC adverse effects due to the AC medications.

One major reason for our results is our new approach to choose individuals who had below normal cognitive scores on neuropsychological assessments but did not manifest clinically

significant cognitive deficiency, i.e., questionable cognitive impairment. In the early stage of cognitive impairment, the preservation of cognitive functions can be attributed to the compensatory effect of non-cholinergic neurons like hyperinnervation of forebrain galaninergic fibers and proliferation of galaninergic receptors [45]. In addition, Acetylcholine (ACh) synthesizing enzyme, choline acetyltransferase, and number of cholinergic neurons increases in early cognitive impairment preserving the cognitive functions [46, 47]. Furthermore, interaction between cholinergic systems and other neuromodulators like norepinephrine, dopamine, serotonin, and GABA play a vital role in modulating the cognitive response in older adults [48]. Consequently, these compensatory mechanisms may preserve the cholinergic enzyme activities and cognitive functions in early stages of cognitive impairment [47].

Since our study sample was at a very early stage of cognitive impairment, the participants might have preserved cognitive functions by initiation of compensatory mechanisms and might have been less susceptible to AC medication side effects. Dumas and Newhouse found that scopolamine (muscarinic ACh receptor antagonist) and mecamylamine (nicotinic ACh receptor antagonist) improved frontal and hippocampal activations as compared to a placebo, providing evidence for cognitive compensation during the early phase of cognitive impairment [49]. In addition, Naveh-Benjamin, Bray and Levy, and Oberauer showed that the comorbidity in older adults may alter the cholinergic functioning and may decrease the ability of the older adults to use the frontal brain mediated compensatory control of cognitive functions that impairs memory [50, 51]. Hence, it is important to note that the older adults with intact cholinergic functions will have a greater compensatory benefit than those with advanced dementia. Our results show that individuals that took AC medications had higher global and domains specific cognitive scores as compared to those who did not take AC medications. In the light of the current evidences, we theorize that our study population of older adults with QCI might have had intact cholinergic functions and benefitted from some level of compensatory response; and the AC medications would have provided additional cognitive benefit by alleviating the comorbidity burden on cognition.

We speculate that the QCI population responds to the therapeutic actions of AC medications, and that the therapeutic effects of AC medications offset any potential iatrogenic AC overload that may manifest cognitive side effects. Supporting our premise, previous studies show that clozapine, a highly potent AC drug, improved attention, reaction time, executive functions, working memory, and verbal fluency among schizophrenic individuals [52]. Recent community-based cohort studies demonstrated an overall decrease in incident dementia among cognitively normal older adults who were treated with anti-hypertensive drugs [53]. Other studies have also provided evidence that anti-hypertensive medication like brain penetrating angiotensin-converting enzyme inhibitors and calcium channel blockers not only decreases the risk of dementia among individuals with hypertension but also slows the progression of dementia [54–56]. These evidences demonstrate that it is likely that the better cognitive scores among individuals with QCI may partly reflect the treatment effect of AC medications, consequently reducing the cognitive burden of comorbidities.

It is important to note that medications such as Captopril, Nifedipine, Diltiazem etc. that have been shown to reduce the overall burden of dementia also have low anticholinergic

properties. This dual action of medications to alleviate the comorbidity effects of dementia while contributing to the anticholinergic burden on brain shows that it is very difficult to separate out the anticholinergic effects of medications from their potential benefits. Hence, the overall impact of AC medications can be measured by their cumulative effects on cognition in the presence of other predictors such as comorbidity. Due to complexity of the cognitive processes and their associations between pathobiological and clinical manifestations, there is limited understanding about the mechanism of specific vulnerability to the AC medications [57]. It might be possible that the neuromodulators might interact with cholinergic systems and mask AC medication effects especially in the early stages of cognitive impairment. Therefore, besides considering independent effects of cholinergic system, it is important to include the interactions between the neuromodulators and cholinergic system. The NACC dataset lacked the information about neuromodulatory systems. This limited the possibility of assessing the neuromodulators' effects on cholinergic system and the cognitive profile of older adults.

The strengths of this study lies in its use of the NACC data from the large population-based prospective study of older adults across the United States. The NACC includes one of the largest numbers of participants in the standardized longitudinal data, which allows us to parcel out a QCI population to study. Additionally, we were able to use a reliable and validated method, ADS, to assess AC load. Furthermore, the NACC data allowed us to take into account various competing causes of cognitive dysfunction in older adults by adjusting for socioeconomic, demographic, health, lifestyle, and genetic factors; thus limiting any potential confounding.

Our study has some limitations. The participants' medication use was collected based on self-reports. In addition, the medication history in the NACC dataset is limited to only two weeks before the visit date. Another limitation of the NACC medication records is the absence of frequency and dosages of medication. Even if this information was available, ADS does not incorporate frequency or the dosages of medications to assess AC drug burden. Moreover, AC drug effect is related to the accumulated burden of AC medications and not only to the dosage of each individual medication. Additionally, the NACC population was selected from the hospital, patient, and physician referrals, which might not be the true representation of the community dwelling older adults in the United States and the results may not generalize to overall population of older adults. Finally, the cross-sectional nature of this study refrain us from evaluating the causality and thus, a longitudinal study is necessary to better assess the long term effects and trends of the AC medications on cognitive performance. Despite these limitations, the NACC dataset is an appropriate resource to assess associations between AC medication burden and cognitive function.

5 Conclusion

These results indicate that older adults with QCI taking medications with AC properties had higher cognitive scores than those not taking AC medications. We cannot definitely rule out the possibility of cholinergic modulators and other unknown factors acting to preserve cognitive reserve in QCI. Nevertheless, it suggests that the therapeutic effects of AC medications might be beneficial to cognition among the QCI population; however, the

relationship between anticholinergic medication use and cognitive functioning in the elderly is complex. Given the lack of significant adverse effects of AC usage in this large sample, it is questionable that AC drug use causes cognitive dysfunction among people with subtle memory and cognitive difficulties. Thus, more research is needed to understand and assess the impact of AC medications on QCI populations. In addition, the future researches should also consider including cognitive modulators in the study to identify clinically meaningful effects of AC exposure groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimer's & Dementia*. 2011; 7:61–73.
2. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. *Arch Med Res*. 2012; 43:600–608. [PubMed: 23159715]
3. Etienne P, Robitaille Y, Wood P, et al. Nucleus basalis neuronal loss, neuritic plaques and choline acetyltransferase activity in advanced Alzheimer's disease. *Neuroscience*. 1986; 19:1279–1291. [PubMed: 3822122]
4. Drachman DA, Sahakian B. Memory and cognitive function in the elderly: a preliminary trial of physostigmine. *Arch Neurol*. 1980; 37:674–675. [PubMed: 7425896]
5. Bird TD, Stranahan S, Sumi S, et al. Alzheimer's disease: choline acetyltransferase activity in brain tissue from clinical and pathological subgroups. *Ann Neurol*. 1983; 14:284–293. [PubMed: 6227276]
6. Henke H, Lang W. Cholinergic enzymes in neocortex, hippocampus and basal forebrain of non-neurological and senile dementia of Alzheimer-type patients. *Brain Res*. 1983; 267:281–291. [PubMed: 6871677]
7. Barnes, CA. Animal models of age-related cognitive decline. In: Boller, F., Grafman, J., editors. *Handbook of Neuropsychology*. Elsevier; Amsterdam: 1990. p. 169-196.
8. Gallagher M, Nicolle MM. Animal models of normal aging: relationship between cognitive decline and markers in hippocampal circuitry. *Behav Brain Res*. 1993; 57:155–162. [PubMed: 7906946]

9. Flaherty JH, Perry HM 3rd, Lynchard GS, et al. Polypharmacy and hospitalization among older home care patients. *J Gerontol A Biol Sci Med Sci*. 2000; 55:M554–9. [PubMed: 11034227]
10. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol A Biol Sci Med Sci*. 2012; 67:698–704. [PubMed: 22219520]
11. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Internal Medicine*. 2015; 175:401–407. [PubMed: 25621434]
12. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging*. 2009; 4:225–233. [PubMed: 19554093]
13. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011; 59:1477–1483. [PubMed: 21707557]
14. Lowry E, Woodman RJ, Soiza RL, et al. Associations between the anticholinergic risk scale score and physical function: potential implications for adverse outcomes in older hospitalized patients. *Journal of the American Medical Directors Association*. 2011; 12:565–572. [PubMed: 21514242]
15. Nabi G, Cody JD, Ellis G, et al. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. *Cochrane Database Syst Rev*. 2006; (4):CD003781. [PubMed: 17054185]
16. Chew ML, Mulsant BH, Pollock BG. Serum anticholinergic activity and cognition in patients with moderate-to-severe dementia. *The American Journal of Geriatric Psychiatry*. 2005; 13:535–538. [PubMed: 15956274]
17. Nebes RD, Pollock BG, Halligan EM, et al. Serum anticholinergic activity and motor performance in elderly persons. *J Gerontol A Biol Sci Med Sci*. 2007; 62:83–85. [PubMed: 17301043]
18. Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging*. 1993; 3:335–348. [PubMed: 8369593]
19. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol*. 1999; 45:358–368. [PubMed: 10072051]
20. Jessen F, Kaduszkiewicz H, Daerr M, et al. Anticholinergic drug use and risk for dementia: target for dementia prevention. *Eur Arch Psychiatry Clin Neurosci*. 2010; 260:111–115.
21. Shah RC, Janos AL, Kline JE, et al. Cognitive decline in older persons initiating anticholinergic medications. *PloS One*. 2013; 8:e64111. [PubMed: 23741303]
22. Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Archives of internal medicine*. 2009; 169:1317–1324. [PubMed: 19636034]
23. Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *Bmj*. 2006; 332:455–459. [PubMed: 16452102]
24. Bottiggi KA, Salazar JC, Yu L, et al. Long-term cognitive impact of anticholinergic medications in older adults. *The American Journal of Geriatric Psychiatry*. 2006; 14:980–984. [PubMed: 17068321]
25. Uusvaara J, Pitkala KH, Kautiainen H, et al. Detailed cognitive function and use of drugs with anticholinergic properties in older people. *Drugs Aging*. 2013; 30:177–182. [PubMed: 23361527]
26. Petersen RC. Mild cognitive impairment or questionable dementia? *Archives of Neurology*. 2000; 57:643–644. [PubMed: 10815128]
27. Daly E, Zaitchik D, Copeland M, et al. Predicting conversion to Alzheimer disease using standardized clinical information. *Archives of Neurology*. 2000; 57:675–680. [PubMed: 10815133]
28. Cronin-Stubbs D, DeKosky ST, Morris JC, et al. Promoting interactions with basic scientists and clinicians: the NIA Alzheimer's Disease Data Coordinating Center. *Stat Med*. 2000; 19:1453–1461. [PubMed: 10844710]
29. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. *Alzheimer Dis Assoc Disord*. 2007; 21:249–258. [PubMed: 17804958]

30. Rosenberg P, Mielke M, Han D, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. *Int J Geriatr Psychiatry*. 2012; 27:1248–1257. [PubMed: 22374884]
31. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol*. 2008; 65:1091–10. [PubMed: 18695059]
32. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a Measure of Drug-Related Anticholinergic Burden: Associations With Serum Anticholinergic Activity. *The Journal of Clinical Pharmacology*. 2006; 46:1481–1486. [PubMed: 17101747]
33. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. *Alzheimer Dis Assoc Disord*. 2006; 20:210–216. [PubMed: 17132964]
34. Hayden KM, Jones RN, Zimmer C, et al. Factor structure of the National Alzheimer's Coordinating Centers uniform dataset neuropsychological battery: an evaluation of invariance between and within groups over time. *Alzheimer Dis Assoc Disord*. 2011; 25:128–137. [PubMed: 21606904]
35. Albert MS, Moss MB, Tanzi R, et al. Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society*. 2001; 7:631–639. [PubMed: 11459114]
36. Price JL, McKeel DW, Buckles VD, et al. Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease. *Neurobiology of aging*. 2009; 30:1026–1036. [PubMed: 19376612]
37. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *Jama*. 2007; 297:1465–1477. [PubMed: 17405972]
38. Uusvaara J, Pitkala KH, Tienari PJ, et al. Association Between Anticholinergic Drugs and Apolipoprotein E ϵ 4 Allele and Poorer Cognitive Function in Older Cardiovascular Patients: A Cross-Sectional Study. *J Am Geriatr Soc*. 2009; 57:427–431. [PubMed: 19278396]
39. Fox C, Livingston G, Maidment ID, et al. The impact of anticholinergic burden in Alzheimer's dementia-the LASER-AD study. *Age Ageing*. 2011; 40:730–735. [PubMed: 21926432]
40. Lechevallier-Michel N, Molimard M, Dartigues J, et al. Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol*. 2005; 59:143–151. [PubMed: 15676035]
41. Sunderland T, Tariot PN, Cohen RM, et al. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls: a dose-response study. *Arch Gen Psychiatry*. 1987; 44:418–426. [PubMed: 3579494]
42. Mulsant BH, Pollock BG, Kirshner M, et al. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch Gen Psychiatry*. 2003; 60:198–203. [PubMed: 12578438]
43. Kochanek KD, Murphy SL, Xu J, et al. Mortality in the United States, 2013. *NCHS data brief*. 2014; 178:1–8.
44. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: The Norwegian EPINCONT Study. *Journal of clinical epidemiology*. 2000; 53:1150–1157. [PubMed: 11106889]
45. Counts SE, He B, Che S, et al. Galanin hyperinnervation upregulates choline acetyltransferase expression in cholinergic basal forebrain neurons in Alzheimer's disease. *Neurodegener Dis*. 2008; 5:228–231. [PubMed: 18322398]
46. Frölich L. The cholinergic pathology in Alzheimer's disease—discrepancies between clinical experience and pathophysiological findings. *J Neural Transm*. 2002; 109:1003–1013. [PubMed: 12111437]
47. Ikonomic MD, Mufson EJ, Wu J, et al. Cholinergic plasticity in hippocampus of individuals with mild cognitive impairment: correlation with Alzheimer's neuropathology. *J Alzheimer's Dis*. 2003; 5:39–48. [PubMed: 12590165]
48. Decker MW, McGaugh JL. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. *Synapse*. 1991; 7:151–168. [PubMed: 1672782]

49. Dumas JA, Newhouse PA. The cholinergic hypothesis of cognitive aging revisited again: cholinergic functional compensation. *Pharmacology Biochemistry and Behavior*. 2011; 99:254–261.
50. Oberauer K. Removing irrelevant information from working memory: a cognitive aging study with the modified Sternberg task. *Journal of Experimental Psychology: Learning, Memory, and Cognition*. 2001; 27:948.
51. Naveh-Benjamin M, Brav TK, Levy O. The associative memory deficit of older adults: the role of strategy utilization. *Psychol Aging*. 2007; 22:202. [PubMed: 17385995]
52. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull*. 1999; 25:233–255. [PubMed: 10416729]
53. Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med*. 2006; 166:1003–1008. [PubMed: 16682574]
54. Hajjar I, Catoe H, Sixta S, et al. Cross-sectional and longitudinal association between antihypertensive medications and cognitive impairment in an elderly population. *J Gerontol A Biol Sci Med Sci*. 2005; 60:67–73. [PubMed: 15741285]
55. Hanon O, Pequignot R, Seux ML, et al. Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints. *J Hypertens*. 2006; 24:2101–2107. [PubMed: 16957572]
56. Ohrui T, Tomita N, Sato-Nakagawa T, et al. Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology*. 2004; 63:1324–1325. [PubMed: 15477567]
57. Lopez OL, Becker JT, Wisniewski S, et al. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002; 72:310–314. [PubMed: 11861686]

Key Points

- Anticholinergic medications given to treat clinical conditions, in older adults in the very early phase of cognitive impairment, appear to improve cognitive functions.
- The cognitive benefit of anticholinergic medications is possibly due to alleviating the comorbidity burden on cognition, and that these individuals may have had intact cholinergic functions and benefitted from some level of compensatory response.

Table 1

Description of baseline characteristics of the study sample stratified by levels of anticholinergic drug use

Variable	AC Drugs			P-value
	No AC Drugs (N=5871, 80%)	Low AC Drugs (N=1148, 16%)	Moderate/high AC Drugs (N=296, 4%)	
Age, (m±sd)	74.5 ± 7.9	76.6 ± 8.2	75.6 ± 7.8	<.001
Male (Sex), n (%)	2896 (49.4)	525 (45.7)	108 (36.5)	<.001
Black (Race), n (%)	776 (13.3)	154 (13.5)	45 (15.3)	.62
Hispanic, n (%)	495 (8.5)	73 (6.4)	27 (9.1)	.05
Education, (m±sd)	14.9 ± 3.6	14.7 ± 3.6	14.6 ± 3.3	.03
Alcohol abuse, n (%)	339 (5.8)	67 (5.9)	11 (3.7)	.33
Smoked >100 cigarette, n (%)	2701 (46.5)	540 (47.6)	136 (46.7)	.78
Body Mass Index, (m±sd)	27.1 ± 5.1	27.5 ± 5.5	27.4 ± 5.7	.02
Living alone, n (%)	1579 (26.9)	358 (31.3)	98 (33.1)	.001
Live Independently, n (%)	4514 (77.2)	841 (73.5)	220 (74.6)	.02
Residence Single, n (%)	5282 (90.2)	988 (86.4)	253 (85.8)	<.001
Married, n (%)	3764 (64.6)	684 (59.7)	167 (56.8)	<.001
1° Relative dementia, n (%)	2387 (41.5)	407 (36.4)	129 (44.6)	.003
Cardiovascular disease, n (%)	1761 (30.0)	573 (49.9)	71 (23.9)	<.001
Cerebrovascular disease, n (%)	674 (11.5)	189 (16.5)	34 (11.5)	<.001
Neurological disease, n (%)	828 (14.1)	169 (14.7)	28 (9.5)	.06
Parkinson's disease, n (%)	185 (3.2)	32 (2.8)	14 (4.8)	.233
Depression, n (%)	1900 (32.6)	489 (44.9)	103 (35.0)	<.001
Metabolic disease, n (%)	4923 (83.9)	970 (84.5)	226 (76.4)	.002
Incontinence, n (%)	898 (15.3)	222 (19.4)	105 (35.5)	<.001
APOE4 genotype, n (%)	1481 (43.2)	297 (41.5)	76 (38.8)	.355
Number of medications, (m±sd)	7.8 ± 4.8	9.2 ± 5.3	8.7 ± 5	.001

AC=Anticholinergic; 1°=First degree, APOE4=allele producing ε4 type of Apolipoprotein E; m=mean; sd =standard deviation.

Table 2

Description of baseline cognitive (global and domain specific) score stratified by levels of anticholinergic drug use

Cognitive Domains	AC Drugs			P-value
	No AC Drugs (N=5871, 80%)	Low AC Drugs (N=1148, 16%)	Moderate/high AC Drugs (N=296, 4%)	
Global (m±sd)	-0.32 ± 0.53	-0.24 ± 0.52	-0.23 ± 0.53	<.001
Memory (m±sd)	-0.80 ± 1.15	-0.68 ± 1.17	-0.63 ± 1.18	<.001
Attention (m±sd)	-0.40 ± 0.88	-0.36 ± 0.85	-0.33 ± 0.89	.04
Executive (m±sd)	0.48 ± 0.80	0.58 ± 0.91	0.56 ± 0.91	<.001
Language (m±sd)	-0.58 ± 0.97	-0.53 ± 0.93	-0.54 ± 0.97	.08

AC=Anticholinergic; m=mean; sd =standard deviation.

Table 3

Multivariable regression analyses of cognitive scores (global and domain-specific) and anticholinergic drug use

Variable	Model 1			Model 2			Model 3			Model 4		
	Estimates ^a	(95 % CI)	p value	Estimates	(95 % CI)	p value	Estimates	(95 % CI)	p value	Estimates	(95 % CI)	p value
No AC drugs	Referent			Referent			Referent			Referent		
Global cognitive scores												
Low AC drugs	0.080 (0.045 to 0.114)		<0.001	0.075 (0.042 to 0.112)		<0.001	0.062 (0.027 to 0.099)		0.001	0.064 (0.020 to 0.110)		0.006
Moderate/high AC drugs	0.091 (0.027 to 0.154)		0.005	0.055 (−0.007 to 0.121)		0.09	0.028 (−0.034 to 0.098)		0.34	0.064 (−0.011 to 0.150)		0.12
R-square	0.004			0.137			0.147			0.152		
Memory scores												
Low AC drugs	0.138 (0.062 to 0.214)		<0.001	0.112 (0.035 to 0.190)		0.004	0.078 (−0.002 to 0.158)		0.06	0.083 (−0.018 to 0.184)		0.11
Moderate/high AC drugs	0.179 (0.039 to 0.318)		0.01	0.118 (−0.033 to 0.270)		0.13	0.051 (−0.110 to 0.210)		0.52	0.027 (−0.164 to 0.217)		0.78
R-square	0.006			0.122			0.129			0.144		
Attention scores												
Low AC drugs	0.031 (−0.027 to 0.088)		0.29	0.048 (−0.012 to 0.110)		0.12	0.040 (−0.022 to 0.102)		0.21	0.031 (−0.046 to 0.109)		0.43
Moderate/high AC drugs	0.071 (−0.035 to 0.177)		0.19	0.160 (0.042 to 0.278)		0.008	0.133 (0.011 to 0.254)		0.03	0.214 (0.070 to 0.360)		0.004
R-square	0.004			0.066			0.070			0.069		
Executive function scores												
Low AC drugs	0.091 (0.040 to 0.150)		0.001	0.063 (0.010 to 0.120)		0.022	0.059 (0.004 to 0.115)		0.04	0.057 (−0.011 to 0.126)		0.10
Moderate/high AC drugs	0.073 (−0.030 to 0.173)		0.15	0.025 (−0.074 to 0.123)		0.624	0.025 (−0.076 to 0.126)		0.63	0.052 (−0.069 to 0.173)		0.39
R-square	0.006			0.097			0.112			0.110		
Language scores												
Low AC drugs	0.062 (−0.001 to 0.125)		0.06	0.070 (0.006 to 0.135)		0.033	0.068 (0.002 to 0.135)		0.05	0.090 (0.008 to 0.173)		0.03
Moderate/high AC drugs	0.049 (−0.067 to 0.165)		0.41	0.078 (−0.049 to 0.205)		0.228	0.062 (−0.068 to 0.193)		0.35	0.092 (−0.064 to 0.249)		0.25
R-square	0.001			0.106			0.107			0.109		

Model 1 is adjusted for age. Model 2 is adjusted for age, sex, race, ethnicity (Hispanic), education level, alcohol abuse, smoking, body mass index, living independence, marriage status, family history of dementia. Model 3 is adjusted for age, sex, race, ethnicity (Hispanic), education level, alcohol abuse, smoking, body mass index, living independence, marriage status, family history of dementia, cardiovascular disease, cerebrovascular disease, Parkinson's disease, neurological disease, hypertension, hypercholesterolemia, diabetes, vitamin B12 deficiency, thyroid disease, incontinence, depression. Model 4 is adjusted for age, sex, race, ethnicity (Hispanic), education level, alcohol abuse, smoking, body mass index, living independence, marriage status, family history of dementia, cardiovascular disease, cerebrovascular disease, Parkinson's disease, neurological disease, hypertension, hypercholesterolemia, diabetes, vitamin B12 deficiency, thyroid disease, incontinence, depression, APOE4

AC anticholinergic, APOE4 allele producing the ε4 type of apolipoprotein E, CI confidence interval

^a Estimates = parameter estimates represent the value of the estimated score difference for the low- and moderate/high-AC groups compared with the no-AC group