Published in final edited form as:

Alzheimer Dis Assoc Disord. 2018 ; 32(3): 262–264. doi:10.1097/WAD.0000000000000251.

Anticholinergic medications and cognitive function in late mid-life

Martin M. Limback-Stokin[*], **Janina Krell-Roesch, PhD**[1], **Kimberly Roesler**[*], **Allison Hansen**[1,*], **Cynthia M. Stonnington, MD**[2], **M'hamed Temkit, PhD**[3], **Richard J. Caselli, MD**[4], and **Yonas E. Geda, MD, MSc**[1,2,4]

[1]Translational neuroscience and Aging Program, Mayo Clinic, Scottsdale, AZ, USA

[2]Department of Psychiatry and Psychology, Mayo Clinic, Scottsdale, AZ, USA

[3]Department of Health Sciences Research, Mayo Clinic, Scottsdale, AZ, USA

[4]Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA

Abstract

We investigated the cross-sectional association between anticholinergics and cognitive function in persons aged ≥ 50 years. Participants underwent neurological examination, neuropsychological testing and were classified into two groups: Those taking (AC+, N = 51) versus not taking anticholinergics (AC−, N = 204). AC+ were comparable to AC− participants by age, sex and education. There was a trend for worse performance in all memory and most executive function tests for AC+, but only the difference in the Paced Auditory Serial Attention Task 2 was significant. There was no dose-effect relationship between anticholinergic use and cognitive test scores. Results were not impacted by APOE ε4 status. In conclusion, we observed a significant difference between AC+ and AC− groups in only one measure of executive function. Thus anticholinergic medications do not appear to impact cognition in this relatively younger sample of late mid-life individuals. A longitudinal study is needed to confirm these findings.

Keywords

Anticholinergics; cognitive function; APOE ε4; late mid-life

INTRODUCTION

Anticholinergic medications are associated with cognitive impairment, particularly executive and memory dysfunction in late life[e.g.,1–5]. Little is known as to whether anticholinergics are also associated with cognitive impairment in late mid-life. The aim of this study was to investigate the cross-sectional associations between anticholinergics and cognitive

Corresponding Author: Yonas E. Geda, MD, MSc, Professor of Neurology and Psychiatry, Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ 85259, USA, Phone: 480-301-4343, geda.yonas@mayo.edu.

[*]These authors were summer undergraduate research students under the mentorship of Professor Geda at Mayo Clinic, Scottsdale, Arizona.

Conflicts of Interest

The authors declare no conflicts of interest.

performance (i.e., memory, executive function, visuospatial function, language) in persons aged ≥ 50 years. We also investigated the impact of APOE ε4 status. We hypothesized that regular anticholinergic use is associated with impaired performance on memory tests, particularly among APOE ε4 carriers; and impaired executive function, which may not be APOE ε4 dependent.

METHODS

Study Design

This cross-sectional study was derived from the ongoing longitudinal Arizona APOE cohort[6] and the Alzheimer's Disease Center cohort studies at Mayo Clinic, Arizona. Briefly, from January 1, 1994 to August 6, 2007, cognitively normal individuals aged ≥ 21 years in Maricopa County were recruited through advertisements for the APOE cohort. From January 1, 2000 to August 6, 2007, cognitively normal residents of Maricopa and Pima Counties aged ≥ 65 years were recruited for the Alzheimer's Disease Center cohort. Candidates were enrolled if they had no confounding medical or neuropsychiatric problems; and did not meet published criteria for mild cognitive impairment, dementia or major depressive disorder. These criteria were determined by a behavioral neurologist (RJC). Demographic, family, and medical data were obtained for participants who also underwent APOE genotyping[7]. All participants provided written informed consent. The study was approved by the institutional review boards of all participating institutions.

Measurement of Exposure to Anticholinergic Medications

Anticholinergic burden was estimated using the Anticholinergic Burden Scale (ABS; ©2012)[8]. Three authors (MMLS, AH, KR) reviewed medications regularly taken by each participant and scored them: 0, no anticholinergics; 1, medications with possible anticholinergic effects; 2 or 3, definite anticholinergics, depending on severity of anticholinergic burden. If a participant reported taking multiple anticholinergics the scores were added. The maximum ABS in our sample was 6. We dichotomized participants into two groups: ABS ≥ 2 (AC+) and ABS ≤ 1 (AC−). Scoring and dichotomization was reviewed by senior investigators (RJC, YEG).

Measurement of Cognitive Function

All participants underwent a neuropsychological test battery[9] assessing four cognitive domains: 1) Memory: Auditory Verbal Learning Test (AVLT), total learning (TL) and long-term memory (LTM); Buschke Selective Reminding Test, total free and cued recall scores; Rey-Osterrieth Complex Figure Test, absolute recall and % recall scores; Benton Visual Retention Test (VRT), total number correct. 2) Executive function: Wisconsin Card Sorting Test, categories completed score, total errors score, perseverative errors score; Paced Auditory Serial Attention Task (PASAT) 3 & 2, second versions total correct scores; Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests, including Digit Span, Mental Arithmetic, and Digit Symbol Substitution (DSS); 3) Language: Boston Naming Test; Controlled Oral Word Association Test; Token Test; WAIS-R vocabulary and similarities subtests; and 4) Visuospatial: Judgment of Line Orientation

(JLO); Facial Recognition Test Short Form; WAIS Block Design subtest; Rey-Osterrieth Complex Figure Test.

Statistical Methods

We adjusted for confounders by frequency matching the exposed (AC+) and unexposed (AC −) group by age (± 5 years), sex and years of education (± 2 years) at 1:4 ratio. We assessed demographic differences between AC+ and AC− groups using T-test and chi-squared test; and differences in neuropschological test scores between groups (AC+ vs. AC−; AC+/APOE ε4+ vs. AC−/APOE ε4−) using T-test and Wilcoxon-rank-sum test. Spearman correlations were used to examine the correlation between neuropsychological test scores and ABS. We conducted multiple regression analyses to model the relationship between neuropsychological test scores with age, ABS and APOE ε4 status. We computed two statistical models: a reduced model including age and ABS, and a full model additionally including the interaction of the coefficients. The reduced model was eventually chosen as partial F-tests indicated that it was as accurate as the full model. In all analyses, we primarily focused on executive function and memory; in secondary analyses we investigated visuospatial function and language. Statistical analysis was conducted using R software version R 3.3.1.

RESULTS

There were no significant differences between AC+ (N = 51) and AC− (N = 204) for age, years of education, sex or APOE ε4 status. AC+ scored significantly lower than AC− on PASAT-2; no other differences were observed (Table 1). There were significant correlations between ABS and few cognitive test scores: AVLT-TL ($r = -0.24$, $p < .001$), AVLT-LTM ($r = -0.27$, $p < .001$), VRT ($r = -0.16$, $p < .01$) and WAIS-DSS ($r = -0.08$, $p < .05$). AC+ performed worse in all visuospatial and most language tests, but only the difference in JLO correct score (mean [SD]; 23.46 [4.1] vs. 24.69 [3.7], $p = 0.026$) was significant. There were no significant differences between AC+/APOEε4+ and AC−/APOε4− for any cognitive test. ABS did not have a significant effect on the regression model in any memory and executive function cognitive test (Table 2); rather it was age that had a main effect ($p < 0.05$). When APOE ε4 status was included as coefficient in the regression models, it did not significantly interact with ABS on any cognitive measure.

DISCUSSION

In this cross-sectional study, we observed a significant difference between AC+ and AC− only in one measure of executive function. However, there was a non-significant trend for worse performance of AC+ as compared to AC− in most memory and executive function tests. There was no consistent dose-effect relationship between ABS and test scores in any of the cognitive domains. Our findings were not impacted by APOE ε4 status.

Anticholinergic burden has been associated with cognitive decline, particularly in individuals aged ≥ 70 years. For example, anticholinergic burden was associated with impaired memory and executive function[3]; as well as with lower cognitive scores and APOE ε4 genotype[2]. The differences between ours and other studies may be due to several reasons;

e.g., our sample was relatively younger; we adjusted for confounders by design and analysis making our results more conservative; we administered domain-specific cognitive tests while other studies used global cognitive tests. Furthermore, investigators reported that injection of low-dose scopolamine led to impaired learning efficiency, working memory and executive function in Aβ+ participants; but no difference was observed between APOE ε4 carries and non-carriers[10]. While their sample was similar to ours in demographics, they conducted a clinical trial and our study was observational.

One strength of our study is that we rigorously measured cognition. Second, we accounted for confounders by matching AC+ and AC− groups for age, sex and education. Furthermore, our data are derived from large, published cohorts. ABS rating was done by three authors and revised multiple times for quality control purpose. Finally, our sample was free of potentially confounding medical or neuropsychiatric problems. A major limitation of our study is its cross-sectional design. Additionally, drug use was self-reported thus we cannot exclude recall bias. Lastly, we conducted analyses on various tests which may raise concerns about multiple comparison bias. However, our analyses were led by a priori hypotheses based on the literature which makes multiple comparison bias a less likely explanation for our findings.

In this study among persons aged ≥ 50 years, anticholinergics were not associated with cognitive impairment. Therefore, our study does not support the growing concern that anticholinergic medication use may be associated with cognitive impairment in late mid-life. However, given our cross-sectional study design, we cannot establish a cause-effect relationship or rule out the possibility that anticholinergics may impact cognitive function in the long-term. Therefore, our results should be considered preliminary until confirmed by a prospective cohort study.

Acknowledgments

Source of Funding:

Support for this research was provided by NIH grants: National Institute of Mental Health (K01 MH068351). The project was also supported by the Robert Wood Johnson Foundation, the Edli Foundation (the Hague, the Netherlands), the Arizona Alzheimer's Disease Core Center and the Arizona Alzheimer's Research Consortium (P30AG19610).

References

1. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ. 2006; 332(7539):455–9. [PubMed: 16452102]
2. Uusvaara J, Pitkala KH, Tienari PJ, Kautiainen H, Tilvis RS, Strandberg TE. Association between anticholinergic drugs and apolipoprotein E epsilon4 allele and poorer cognitive function in older cardiovascular patients: a cross-sectional study. J Am Geriatr Soc. 2009; 57(3):427–31. [PubMed: 19278396]
3. Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008; 56(12):2203–10. [PubMed: 19093918]

4. Carrière 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. Arch Intern Med. 2009; 169(14):1317–24. [PubMed: 19636034]

5. Broks P, Preston GC, Traub M, Poppleton P, Ward C, Stahl SM. Modelling dementia: effects of scopolamine on memory and attention. Neuropsychologia. 1988; 26(5):685–700. [PubMed: 3211287]

6. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med. 2009; 361(3):255–263. [PubMed: 19605830]

7. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res. 1990; 31(3):545–8. [PubMed: 2341813]

8. Regenstrief Institute, Inc. The Aging Brain Program, Indiana University Center for Aging Research. Anticholinergic Cognitive Burden Scale. ©2012.

9. Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4. New York: Oxford University Press; 2004.

10. Lim YY, Maruff P, Schindler R, et al. Disruption of cholinergic neurotransmission exacerbates Aβ-related cognitive impairment in preclinical Alzheimer's disease. Neurobiol Aging. 2015; 36(10): 2709–15. [PubMed: 26233262]

Table 1

Characteristics of participants, stratified by anticholinergic status (AC+ vs. AC−)

	AC+ (n = 51) Mean (SD)	AC− (n = 204) Mean (SD)	p
Age, years	61.7 (7.5)	61.8 (7.2)	0.927
Education, years	15.8 (2.5)	15.7 (2.4)	0.847
Female sex, %	73	73	1
APOE ε4 carriers, %	35	41	0.262
Memory			
AVLT-TL	48.8 (10.4)	48.1 (9.0)	0.55
AVLT-LTM	9.2 (3.4)	9.5 (3.2)	0.71
SRT-free-total	89.4 (12.4)	87.96 (11.0)	0.31
SRT-cued-total	22.5 (12.4)	23.7 (10.7)	0.35
CFT-recall	17.9 (7.2)	17.9 (6.5)	0.89
CFT-recall-copy (%)	0.5 (0.2)	0.5 (0.2)	0.85
VRT	6.5 (2.1)	6.8 (1.99)	0.35
Executive			
WCST-Cat	4.7 (1.9)	4.9 (1.7)	0.25
WCST-errors	34.1 (22.3)	31.9 (20.6)	0.27
WCST-per-err	15.9 (11.6)	16.0 (11.0)	0.48
PASAT-3	39.9 (17.2)	44.1 (13.2)	0.07
PASAT-2	30.5 (13.9)	34.2 (12.7)	0.046*
WAIS-Dig-Sp	10.8 (2.9)	11.3 (2.8)	0.16
WAIS-Arith	11.1 (2.8)	11.8 (2.6)	0.06
WAIS-DSS	12.3 (2.1)	12.9 (2.4)	0.07

Comparison between AC+ and AC− groups using t-test (for continuous variables) and chi-squared test (for female sex % and APOE ε4 carriers %); SD = standard deviation;

* = $p < .05$;

AC+ = taking anticholinergics; AC− = not taking anticholinergics. AVLT-TL = Auditory Verbal Learning Test, total learning; AVLT-LTM = Auditory Verbal Learning Test, long-term memory; SRT-free-total = Buschke Selective Reminding Test, total free; SRT-cued-total = Buschke Selective Reminding Test, total cued; CFT-recall = Rey-Osterrieth Complex Figure Test, absolute recall; CFT-recall-copy (%) = Rey-Osterrieth Complex Figure Test, % recall copy score; VRT = Benton Visual Retention Test, total number correct; WCST-Cat = Wisconsin Card Sorting Test, categories completed score; WCST-errors = Wisconsin Card Sorting Test, total errors score; WCST-per-err = Wisconsin Card Sorting Test, perseverative errors score; PASAT-3 = Paced Auditory Serial Attention Task 3 total correct score; PASAT-2 = Paced Auditory Serial Attention Task 2 total correct score; WAIS-Dig-Sp = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Digit Span; WAIS-Arith = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Mental Arithmetic; WAIS-DSS = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Digit Symbol Substitution.

Table 2

Association between anticholinergic status and memory and executive function test scores (multiple linear regressions)

	Reduced model		Anticholinergic status		
Cognitive test	**RSE**	**R^2**	**Effect estimate**	**CI**	**p**
Memory					
AVLT-TL	8.951	0.067	0.698	−2.06 – 3.46	0.62
AVLT-LTM	3.112	0.079	−0.269	−1.23 – 0.691	0.58
SRT-free-total	11.05	0.050	1.136	−2.50 – 4.77	0.54
SRT-cued-total	10.76	0.050	−0.879	−4.42 – 2.66	0.63
CFT-recall	6.57	0.019	−0.050	−2.08 – 1.98	0.97
CFT-recall-copy (%)	0.176	0.015	−0.00111	−0.0555– 0.0532	0.97
VRT	1.939	0.075	−0.346	−0.949 – 0.257	0.26
Executive					
WCST-Cat	1.654	0.075	−0.253	−0.797 – 0.292	0.36
WCST-errors	20.26	0.063	2.87	−3.80 – 9.53	0.397
WCST-per-err	10.81	0.055	0.280	−3.28 – 3.84	0.88
PASAT-3	13.95	0.038	−4.54	−9.18 – 0.0899	0.055
PASAT-2	12.9	0.019	−3.89	−8.19 – 0.404	0.076
WAIS-Dig-Sp	2.792	0.010	−0.436	−1.30 – 0.425	0.32
WAIS-Arith	2.656	0.0068	−0.654	−1.47 – 0.165	0.12
WAIS-DSS	2.201	0.087	−0.496	−1.22 – 0.228	0.18

RSE = Residual standard error; R^2 = Adjusted R squared (coefficient of determination); CI = 95% confidence interval; p = p-value. AVLT-TL = Auditory Verbal Learning Test, total learning; AVLT-LTM = Auditory Verbal Learning Test, long-term memory; SRT-free-total = Buschke Selective Reminding Test, total free; SRT-cued-total = Buschke Selective Reminding Test, total cued; CFT-recall = Rey-Osterrieth Complex Figure Test, absolute recall; CFT-recall-copy (%) = Rey-Osterrieth Complex Figure Test, % recall copy score; VRT = Benton Visual Retention Test, total number correct; WCST-Cat = Wisconsin Card Sorting Test, categories completed score; WCST-errors = Wisconsin Card Sorting Test, total errors score; WCST-per-err = Wisconsin Card Sorting Test, perseverative errors score; PASAT-3 = Paced Auditory Serial Attention Task 3 total correct score; PASAT-2 = Paced Auditory Serial Attention Task 2 total correct score; WAIS-Dig-Sp = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Digit Span; WAIS-Arith = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Mental Arithmetic; WAIS-DSS = Age-scaled scores of the Wechsler Adult Intelligence Scale-Revised subtests, Digit Symbol Substitution.