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Donepezil-associated survival benefits among Alzheimer's disease patients are retained but not enhanced during COVID-19 infections

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Abstract

Background and Aim: Donepezil is a front-line treatment for Alzheimer's disease. Donepezil treatment is associated with decreased risk of all-cause mortality. Specific protection is observed in pneumonia and cardiovascular disease. We hypothesized that donepezil treatment would improve mortality among Alzheimer's patients following infection with COVID-19. The objective of this study is to assess the influence of ongoing donepezil treatment on survival in Alzheimer's disease patients after polymerase chain reaction (PCR)-confirmed COVID-19 infection.

Methods: This is a retrospective cohort study. We conducted a national survey of Veterans with Alzheimer's disease to assess the influence of ongoing donepezil treatment on survival in Alzheimer's disease patients after PCR-confirmed COVID-19 infection. We assessed all-cause 30-day mortality stratified by COVID-19 infection and donepezil use, estimating odds ratios using multivariate logistic regression.

Results: Among people with Alzheimer's disease and COVID-19, all-cause 30-day mortality was 29% (47/163) for people taking donepezil compared with 38% (159/419) for those who were not. Among people with Alzheimer's disease without COVID-19, all-cause 30-day mortality was 5% (189/4189) for people taking donepezil compared with 7% (712/10,241) for those who were not. Adjusting for covariates, the decrease in mortality associated with donepezil did not differ between people with and without COVID-19 (interaction $p = 0.710$)

Conclusion: The known survival benefits of donepezil were retained but not found to be specific to COVID-19 among people with Alzheimer's disease.

Keywords: Alzheimer's disease, COVID-19, donepezil, drug repurposing, retrospective analysis, SARS-CoV-2, veterans

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Introduction

Even before the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, Alzheimer's disease (AD) was the fifth leading cause of death for Americans aged 65 years or older.[1] AD patients tend to have a number of comorbid conditions such as pulmonary disease, hypertension/cardiovascular disease, diabetes, and kidney dysfunction.[2,3] AD and AD-associated comorbidities are also risk factors for the fatal COVID-19 disease. A retrospective cohort study of nearly 2 million US adults found that AD and related dementia was an independent risk factor for severe disease following infection with SARS-CoV-2.[4]

The acetylcholinesterase (AChE) antagonist donepezil is a widely used AD therapeutic.[5] Large

observational cohort studies show donepezil reduces all-cause mortality for AD patients, with protection most evident in pneumonia and cardiovascular disease.[6–11] The mechanism(s) responsible for decreased mortality are unclear. As an AChE antagonist, donepezil increases the availability of acetylcholine, which regulates both acute and chronic inflammation in a brain-immune cell-mediated anti-inflammatory circuit.[12] Donepezil is also an agonist of the intracellular sigma-1 receptor. Sigma-1 activity appears to regulate multiple aspects of physical and neurologic functions during later lafe.[13] Sigma-1 receptor agonists are currently being explored for SARS-CoV-2 therapeutic potential.[14,15]

Given the observational cohort studies showing that donepezil treatment decreases all-cause mortality, particularly in the case in pneumonia, we hypothesized that donepezil usage would be associated with decreased mortality following COVID-19 infection.[16] To test this hypothesis, we conducted a retrospective cohort study of US Veterans diagnosed with AD, comparing mortality among individuals with positive and negative SARS-CoV-2 polymerase chain reaction (PCR) tests who were and were not taking donepezil.

Methods

Study design and data sources

We conducted a retrospective cohort study of Veterans tested for SARS-CoV-2 in the VA healthcare system (henceforward Veterans) from January 1, 2019, through December 31, 2021. Data were extracted from the VHA's Corporate Data Warehouse, the VHA's Vital Status File, and the VA COVID-19 Shared Data Resource.

Case definitions and characterization

Inclusion criteria were Veterans with a diagnosis of AD as ascertained by *International Classification of Diseases* (ICD) codes (Supplemental Table 1) who were tested for SARS-CoV-2 in the VA. Exclusion criteria were Veterans who were lost to follow-up within the VA healthcare system within 30 days following their incident positive SARS-CoV-2 test.

Veterans with a COVID-19 infection were defined as those having a positive SARS-CoV-2 PCR test; only the first positive test was assessed. We characterized the cohort based on the following factors: age, sex, self-reported race and ethnicity, underlying comorbid conditions including other types of dementia, the Charlson Comorbidity Index (CCI) score based on ICD codes,[17] documented vaccination status at the time of a positive SARS-CoV-2 test result, and prescriptions for donepezil and memantine, rivastigmine, or galantamine. Patients were considered to be residents of VA nursing homes, called Community Living Centers (CLCs), if their positive SARS-CoV-2 test occurred while admitted to or within 2 weeks following discharge from a CLC. At the time of their positive SARS-CoV-2 tests, Veterans were considered vaccinated if at least 2 weeks had passed since a dose of the Janssen vaccine (Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson, New Brunswick, NJ) or after the second dose of either mRNA vaccine for COVID-19. Those who received a third dose of either mRNA vaccine before their first positive SARS-CoV-2 test were considered boosted. The outcome was all-cause mortality in the 30 days following a positive SARS-CoV-2 test.

We also assessed Veterans with AD who had neither a positive SARS-CoV-2 PCR test nor a COVID-19 diagnosis during the study period. Veterans who did not have a positive SARS-CoV-2 test but had an ICD, Tenth Revision, code indicating COVID infection were excluded. Veterans lost to VA healthcare follow-up within 30 days following their incident negative SARS-CoV-2 PCR test were excluded. We used incident negative SARS-CoV-2 PCR tests to assess the following characteristics and outcomes that had a temporal association: CLC resident status, vaccination status, and all-cause 30-day mortality.

Statistical analysis

Differences between Veterans with a COVID-19 infection who were and were not taking donepezil were assessed using Welch two-sample *t* tests for continuous data and Pearson's chi-square tests for categorical data. Mortality rates were compared using Pearson's chi-square tests. A multivariable logistic regression model was used to estimate odds ratios (ORs) and 95% confidence intervals for all-cause 30-day mortality that included age, sex, race, ethnicity, CCI score,

CLC stay, donepezil use, concurrent use of memantine, concurrent use of rivastigmine, concurrent use of galantamine, and COVID-19 infection. The interaction of donepezil treatment and COVID-19 infection was the effect of interest, assessing if the mortality risk of COVID-19 differed between those prescribed donepezil and those who were not. Statistical analyses were performed using *R* (version 3.5.1; Vienna, Austria) including functions from additional packages.[18]

Results

Clinical characteristics

During the study period, which accounted for the first 2 years of the COVID-19 pandemic, 582 Veterans with AD had a positive SARS-CoV-2 PCR test. The population was 96% male with a mean age of 81.0 (±9.2) years (Table 1). In addition to AD, people in the cohort had additional diagnoses of unspecified dementia (71%) and other degenerative diseases of the nervous system (46%). At the time of their incident positive SARS-CoV-2 PCR test, 28% (163/582) of people in the cohort had an active prescription for donepezil. A higher percentage of people taking donepezil had concurrent prescriptions for memantine compared to those not taking donepezil (31% *versus* 11%, respectively; $p < 0.001$).

All-cause mortality rates

Among people with a positive SARS-CoV-2 test, all-cause 30-day mortality was lower in those taking donepezil than that in those who were not (29% *versus* 38%; chi-square $p = 0.049$). Given that previous literature has indicated that donepezil reduces all-cause mortality, we also evaluated people with AD without evidence of a COVID-19 infection during the study period. The demographics and comorbid conditions for this population were similar to those that had a positive SARS-CoV-2 test (Supplemental Table 2). Among people with no evidence of a COVID-19 infection during the study period, all-cause 30-day mortality was lower among those taking donepezil than that among those who were not (5% *versus* 7%; chi-square $p < 0.01$). In a multivariate logistic regression model, the decrease in mortality associated with donepezil did not differ between people with and without COVID-19 (adjusted OR = 0.67 *versus* 0.73 for those with *versus* without COVID-19; interaction OR = 1.060, $p = 0.710$; Table 2).

Discussion

Among a national cohort of Veterans with AD, donepezil treatment was associated with a significant decrease in mortality. The decreased risk of death clearly extended to individuals with diagnosed COVID-19 infections. To our knowledge, this is the first study to evaluate the influence of donepezil on mortality following COVID-19 infection among people with AD.

The multivariate model presented here is consistent with previous literature describing COVID-19, indicating a greater risk of all-cause mortality with increasing age, especially among men.[4,18,19] The large proportion of men in our cohort, consistent with a Veteran population, may have augmented the strength of the association. Previous studies also reported that cognitive impairment, and specifically AD, increased the risk of COVID-19 infection and severe outcomes among older adults.[20–22]

The current study expands on previous work showing that people taking donepezil have a decreased risk of death from all causes, including pneumonia and cardiovascular events,[6–11] which are themselves major factors in fatal COVID-19 disease.[16,23] Our findings indicate that donepezil confers a survival benefit among AD patients, with a similar protective effect among those with and without COVID-19 infections.

Particularly early in the pandemic, clinicians used several medications with anti-inflammatory properties in an attempt to treat people with severe COVID-19 infections. The most successful strategy used corticosteroids, which is now included in the standard of care for people with a severe disease.[24,25] The evidence supporting other agents, including hydroxychloroquine, ivermectin, azithromycin, and doxycycline, has not borne out.[26] The data presented here show that while donepezil is associated with a survival benefit among people with AD, the effect size did not differ between people with and without COVID-19 infections using the multivariate logistic regression model.

The mechanisms through which donepezil improves survival may relate its function as an

Table 1. Characteristics of Veterans with Alzheimer's disease and a positive SARS-CoV-2 PCR test.

Characteristics	All (N = 582)	Donepezil (*n* = 163)	No donepezil (*n* = 419)	*P* value[a]
Age, mean (±SD)[b]	81.0 ± 9.2	80.3 ± 7.6	81.3 ± 9.7	0.21
Male sex, no. (%)[c]	559 (96%)	156 (96%)	403 (96%)	0.98
Race				0.68
White	407 (70%)	111 (68%)	296 (71%)	
Black	129 (22%)	40 (25%)	89 (21%)	
Other[d]	46 (8%)	12 (7%)	34 (8%)	
Ethnicity				0.69
Not Hispanic	514 (88%)	143 (88%)	371 (89%)	
Hispanic	55 (9%)	15 (9%)	40 (10%)	
Other[d]	13 (2%)	5 (3%)	8 (2%)	
Charlson Comorbidity Index, mean (±SD)[b]	3.15 ± 2.3	3.31 ± 2.0	3.09 ± 2.4	0.27
Common comorbid conditions				
Diabetes mellitus	235 (40%)	74 (45%)	161 (38%)	0.15
Pulmonary disease	133 (23%)	33 (20%)	100 (24%)	0.41
Stroke	125 (21%)	36 (22%)	89 (21%)	0.91
Renal disease	113 (19%)	29 (18%)	84 (20%)	0.62
Heart disease	97 (17%)	32 (20%)	65 (16%)	0.28
Cancer	85 (15%)	26 (16%)	59 (14%)	0.66
Peripheral vascular disease	80 (14%)	24 (15%)	56 (13%)	0.77
Liver disease	28 (5%)	9 (6%)	19 (5%)	0.78
HIV	0 (0%)	0 (0%)	0 (0%)	–
Other types of dementia[e]				
Vascular dementia	188 (32%)	58 (36%)	130 (31%)	0.34
Unspecified dementia	413 (71%)	117 (72%)	296 (71%)	0.87
Other degenerative diseases of the nervous system	267 (46%)	80 (49%)	187 (45%)	0.38
Memantine prescription	95 (16%)	50 (31%)	45 (11%)	<0.001
Rivastigmine prescription	11 (2%)	0 (0%)	11 (3%)	0.08
Galantamine prescription	13 (2%)	0 (0%)	13 (3%)	0.05
Completed initial COVID-19 vaccine series before a positive test	81 (14%)	33 (20%)	48 (11%)	0.10
Received ⩾1 booster before a positive test	11 (2%)	3 (2%)	8 (2%)	0.13
Community Living Center resident[b]	40 (7%)	11 (7%)	29 (7%)	1.00
Mechanical ventilation within 30 days of a positive SARS-CoV-2 PCR test	32 (5%)	8 (5%)	24 (6%)	0.85
All-cause 30-day mortality following a positive SARS-CoV-2 PCR test	206 (35%)	47 (29%)	159 (38%)	0.0396

PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.
[a]Compares Veterans with Alzheimer's disease who were taking donepezil to those who were not.
[b]Community Living Centers are Veterans Affairs postacute and long-term care facilities.
[c]All values written as no. (%) unless otherwise indicated.
[d]For race, includes American Indian, Alaska Native, Asian, Native Hawaiian or Pacific Islander and unknown; for ethnicity, includes unknown.
[e]As determined by the *International Classification of Disease* (ICD) Codes and detailed in Supplemental Table 1.

Table 2. Odds ratio for 30-day all-cause mortality among patients with Alzheimer's dementia.

Characteristics	Adjusted odds ratio[a]	95% Confidence interval	*p* Value
Age (years)	1.074	1.065, 1.082	<0.001
Sex (reference = male)	0.479	0.271, 0.785	0.006
Race & ethnicity (reference: White, non-Hispanic)			
Black, non-Hispanic	0.942	0.789, 1.120	0.503
Hispanic	1.111	0.920, 1.336	0.267
Other[c]	0.971	0.753, 1.237	0.816
Charlson Comorbidity Index score (1-point increments)	1.026	1.001, 1.050	0.041
CLC resident	1.258	1.068, 1.477	0.006
Vaccination status (complete initial series *versus* unvaccinated/not complete initial vaccine series)	0.667	0.555, 0.797	<0.001
Donepezil use	0.674	0.567, 0.799	<0.001
Memantine use	0.955	0.792, 1.145	0.624
Rivastigmine use	0.861	0.478, 1.437	0.590
Galantamine use	0.909	0.619, 1.295	0.613
SARS-CoV-2 PCR test (reference = negative)	8.829	7.041, 11.051	<0.001
Interaction between donepezil and positive SARS-CoV-2 PCR test result	1.087[b]	0.696, 1.684	0.710

CLC, Community Living Centers; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Adjusted odds ratios estimated in logistic models adjusting for age, sex, Charlson Comorbidity Index score, being a CLC resident, have a positive SARS-CoV-2 test, and use of memantine and/or donepezil.
[b]Interaction odds ratio estimates the multiplicative difference in the donepezil odds ratio for mortality among people with Alzheimer's disease who did *versus* did not have a COVID-19 infection.
cRace includes American Indian, Alaska Native, Asian, Native Hawaiian or Pacific Islander and unknown; for Ethnicity includes unknown.

AChE antagonist, as well as sigma-1 receptor agonist activity. If donepezil was acting to reduce viral replication via the sigma-1 receptor, we would have anticipated decreased mortality among those with COVID-19 infections compared with uninfected patients. The similar benefit implies that the mechanism of protection afforded by donepezil does not involve a specific antiviral activity associated with the sigma-1 agonist activity, such as has been described for fluvoxamine.[27] The possibility remains that donepezil-mediated protection involves a sigma-1 agonist function distinct from any effect on viral replication. The ubiquitously expressed sigma-1 mediates multiple diverse biologic activities. These include regulating acute cellular stress, autophagy, and apoptosis[14,15]; neuroplasticity, inflammation, and repair[28,29]; and macrophage inflammatory cytokine production, polarization, and function.[30,31] Loss of sigma-1 activity also appears to increase age-related physical and neurologic pathology,[13] and sigma-1 receptor agonists are currently being explored as a therapeutic strategy to treat AD.[32] These wide-spread effects make it impossible to discount the possibility that donepezil mediates protection in part via sigma-1 receptor agonist activity.

Our study has important limitations. First, VA healthcare users are predominantly White non-Hispanic male Veterans with a greater burden of chronic medical conditions than non-Veteran populations in the United States.[33,34] This may limit generalization of our results. Second, this study

relied on administrative data limited to the VA healthcare system, thereby missing Veterans who received SARS-CoV-2 tests and healthcare at non-VA venues. To mitigate this, we excluded Veterans who were lost to follow-up within 30 days of their incident positive SARS-CoV-2 PCR test or those without evidence of a COVID-19 infection, within 30 days of their incident negative test. Third, our study was limited to Veterans with an AD diagnosis. Within this group, we were unable to determine the severity or stage of the disease. Furthermore, the influence of donepezil on COVID-19-related mortality among Veterans taking this for conditions other than AD (i.e. off-label usage) was not assessed.[35] Finally, data only address mortality rather than morbidity. The study population included primarily outpatients, making it difficult to determine exactly when a patient was considered 'recovered.' The number of patients hospitalized or admitted to an intensive care unit unit was too small to make any statistically valid conclusions. Due to these limitations, results should be interpreted cautiously, especially regarding women and minorities who are greatly underrepresented in the current patient population.

Conclusions

The results of our national retrospective cohort study indicated that the established mortality benefits conferred by donepezil are retained but not enhanced during COVID-19 infection. The data presented here do not determine the mechanism of protection, but they do add to the growing body of literature showing the association between donepezil treatment and generalizable health benefits.

Declarations

Ethics approval and consent to participate

The Institutional Review Board at the VA Northeast Ohio Healthcare System approved the study protocol (CY15-037) and granted a waiver of informed consent because the research was no more than minimal risk and the waiver would not adversely affect the participants' rights and welfare.

Consent for publication

Not applicable.

Author contributions

Elizabeth A. Edmiston: Formal analysis; Investigation; Methodology; Writing – original draft.

Taissa A. Bej: Data curation; Formal analysis; Methodology; Project administration; Visualization; Writing – review & editing.

Brigid Wilson: Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Robin L. P. Jump: Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: None of the authors have relevant conflicts of interest to disclose. R.L.P.J. has received research funding from Merck Corporation; she has also participated in advisory boards for Pfizer and Merck.

Availability of data and materials

The data set generated during this study is not publicly available but is available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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