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Treatment Practices of Mild Cognitive Impairment in California Alzheimer's Disease Centers

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Abstract

Objectives: To examine “real world” treatments for patients with Mild Cognitive Impairment (MCI).

Design: Cross-sectional.

Setting: California Department of Public Health Alzheimer's Disease (AD) Research Centers of California.

Participants: Five hundred and seventy-eight patients diagnosed with MCI.

Measurements: All patients underwent comprehensive neurological and neuropsychological evaluations. Logistic regression models were used to determine patient characteristics associated with use of anti-AD medications, statins, antioxidants, and folic acid.

Results: One hundred and sixty-six patients (28.7%) were taking anti-AD medications; use was associated with greater functional impairment, higher education, MCI subtype, and older age ($p < 0.05$ for all). Two hundred and fifty-two patients (43.6%) were taking statins; use was associated with diabetes, hypertension, myocardial infarct, male gender, and MCI subtype ($p < 0.05$ for all). One hundred and fifteen patients (19.9%) were taking antioxidants; use was associated with higher education, diabetes, and varied by site ($p < 0.05$ for all). Thirty-seven patients (6.4%) were taking folic acid; use was associated with non-white race, male gender, and greater functional impairment ($p < 0.05$ for all).

Conclusion: This study suggests that MCI patients are frequently being treated with “off-label” ChIs and memantine, as well as other possible cognitive enhancing drugs. Further investigation about the effect of treatment patterns on the clinical course of MCI is needed.

Keywords

Alzheimer's disease; mild cognitive impairment; aging, medications; cholinesterase inhibitors

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INTRODUCTION

Mild cognitive impairment (MCI) is a cognitive syndrome that lies on the continuum between normal aging and dementia. MCI is very common and affects approximately 19% of elders over 65 years of age¹. Compared to elders with normal cognition, MCI patients are at a 3-5 times increased risk for developing Alzheimer's Disease (AD) and have a greater rate of mortality^{2, 3}. With the aging of many countries' populations and subsequent expansion of MCI prevalence and incidence, finding treatments that improve MCI symptoms and delay the possible progression of MCI to dementia is essential.

While there are several FDA-approved medications for AD, there are no approved medications for patients with MCI. For AD treatment, clinical practice guidelines suggest a trial of a cholinesterase inhibitor (ChI) for mild to moderate severity and memantine for moderate to severe disease⁴. While controversial, some studies have suggested that statins or antioxidants may be beneficial for prevention of cognitive impairment⁵⁻¹⁰. High levels of homocysteine and low levels of folic acid have been associated with cognitive impairment, suggesting that homocysteine-reducing vitamins, such as folic acid, may prevent cognitive decline¹¹.

In the absence of specific guidelines or FDA approved medications, it is valuable to know the treatment patterns currently employed by health care professionals for patients with MCI. This study investigates current "real world" treatment practices for MCI patients evaluated at the California Department of Public Health Alzheimer's Disease Research Centers of California. In addition, this study explores which patient characteristics are associated with medication use.

METHODS

Setting

Patients were evaluated at one of the ten California Department of Public Health's Alzheimer's Disease Research Centers of California (ARCCs). The ARCCs are state-funded clinics located at university medical centers within California. The sites include the University of Southern California (2 sites), Stanford University, and the University of California at Davis (2 sites), Irvine, Los Angeles, San Diego, and San Francisco (2 sites). The ARCC sites have been closely collaborating and using a standardized research data collection protocol (Minimum Uniform Data Set [MUDS]) for over 10 years¹². Demographic, diagnostic, and medication data were collected using the MUDS. Data are processed centrally through the Institute for Health and Aging at the University of California, San Francisco. To increase inter-site reliability and accuracy, training and recalibration exercises are held with case reports, videos, and autopsy findings^{13, 14}. All ARCCs obtain site specific IRB approval and receive informed consent from patients for data collection.

We studied patients diagnosed with cognitive impairment not meeting criteria for dementia (N = 578) between July 2006 and April 2008. This diagnosis includes individuals diagnosed with amnesic disorder¹⁵, single mild non-memory cognitive impairment¹⁵, mild neurocognitive disorder¹⁵, MCI based on Petersen criteria², and MCI based on the Alzheimer's Disease Cooperative Study (ADCS) criteria¹⁶. Patients could be diagnosed with more than one of these syndromes. For the purposes of this study, we categorized all of these diagnoses as MCI. MCI diagnoses based on either Petersen or ADCS criteria were analyzed together.

Measurements

All ARCC patients underwent a comprehensive evaluation including medical history, neurological examination, and neuropsychological assessment. We collected information on age, gender, race, years of education, and medical history. Following the evaluation, clinical

diagnoses were determined at multidisciplinary conferences. These conferences typically consisted of neurologists, neuropsychologists, nurses, and psychiatrists. Functional status was reported with the Blessed-Roth Dementia Rating Scale (BRDRS), which is scored from 0 to 17 with higher scores indicating greater difficulty¹⁷. Cognitive function was reported with the Mini Mental Status Examination (MMSE), which is scored from 0 to 30 with higher scores indicating higher cognitive function¹⁸.

Medications

All current and past medication use was recorded. Patients and caregivers were asked about all medications prescribed either in the ARCC or by outside physicians, as well as medications taken without physician prescription. Patients were encouraged to bring medication containers to the ARCC for documentation. For the ARCCs (n = 3) which are also associated with Veterans Affairs Medical Centers with computerized medical records, records were reviewed for medication prescriptions. Medication data was coded in categories according to the Cerner Multum Lexicon¹⁹. Anti-AD medications included memantine and the ChIs: donepezil, galantamine, and rivastigmine. No patients were taking tacrine. Antioxidants included vitamin E, ascorbic acid (alone or in combinations), and coenzyme Q10. Participants who were only taking standard multivitamins without supplementation with antioxidants were not considered in the antioxidant category. Statins included lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin. Use of the homocysteine lowering vitamin, folic acid, and ginkgo biloba was documented.

Statistical Analysis

In initial bivariate analyses, we used the Wilcoxon test for continuous variables and the Pearson χ^2 test for categorical variables to compare patient characteristics among those patients taking or not taking medications. Separate multivariate logistic regression models were performed to determine the likelihood of ever taking an anti-AD medication, a statin, an antioxidant, or folic acid. Since only 6 participants were taking ginkgo biloba, we did not conduct a model for its use. Items chosen as covariates for the multivariate analyses included factors shown previously in the literature to be associated with cognitive status or medication treatment and that had a $p < 0.20$ significance in the bivariate models^{3, 4, 20}. These covariates included age (per standard deviation of 9.9 years), education (no more than high school, some college education, college education and beyond), race (white vs. non-white), gender, clinic site, MMSE score (per standard deviation of 2.8 points), BRDRS score (per standard deviation of 2.2 points), MCI type sub-diagnosis, and history of hypertension, myocardial infarction (MI), stroke or transient ischemic attack (TIA), and diabetes. Across site variation was assessed using a dummy variable in the models. All models were checked for goodness of fit with the Hosmer-Lemeshow goodness of fit test. Variance inflation factors were calculated to test for collinearity between variables in each model.

RESULTS

The mean age of the 578 MCI patients was 75.1 ± 9.9 years, mean education was 14.9 ± 3.8 years, mean MMSE score was 26.6 ± 2.8 points, mean BRDRS score was 1.7 ± 2.2 points, 447 (77.3%) patients were white, and 276 (47.8%) were female. One hundred and thirteen (19.6%) patients had a history of diabetes, 366 (63.3%) had a history of hypertension, 45 (7.8%) had a history of MI, and 75 (13.0%) had a history of stroke or TIA. There were 154 (26.7%) patients diagnosed with amnesic disorder, 64 (11.1%) diagnosed with single non-memory cognitive impairment, 209 (36.2%) diagnosed with mild neurocognitive disorder, and 240 (41.5%) diagnosed with Petersen or ADOS criteria. At the time of this study, 103 (17.8%) patients had taken or were currently taking ChIs, 21 (3.6%) had taken or were taking memantine, and 42 (7.3%) patients had taken both medications, totaling 166 (28.7%) patients having ever taken

an anti-AD medication (Table 1). Statins were/had been taken by 252 (43.6%) patients, antioxidants by 115 (19.9%) patients, and folic acid by 37 (6.4%) patients (Table 1). Of the 166 patients taking anti-AD medications, there were 77 (46.4%) patients taking both anti-AD medications and statins, 39 (23.5%) patients taking both anti-AD medications and antioxidants, and 15 (9.0%) patients taking both anti-AD medications and folic acid (Table 1).

Compared to those who had never taken anti-AD medications, patients currently/previously taking anti-AD medications were older (77.5 ± 7.2 years vs. 74.2 ± 10.6 years, $p < 0.001$), had a lower MMSE score (26.1 ± 2.9 vs. 26.8 ± 2.7 , $p = 0.006$), had a higher BRDRS score (2.3 ± 2.2 vs. 1.4 ± 2.1 , $p < 0.001$), and varied by site ($p < 0.001$) (Table 2). Of the patients taking anti-AD medications, 35.5% had an amnestic disorder as compared to 23.1% of those patients not taking anti-AD medications ($p = 0.002$) (Table 2). There were no other statistically significant differences of anti-AD medication use among MCI Rtype. Patients currently/previously taking statins were more likely to be male (57.9% vs. 46.0%, $p = 0.003$) and have a history of diabetes (29.0% vs. 12.3%, $p < 0.001$), hypertension (75.8% vs. 53.7%, $p < 0.001$), or MI (13.9% vs. 3.1%, $p < 0.001$) as compared to those who were not taking statins. The patients taking statins were less likely to have a mild neurocognitive disorder diagnosis than those patients who were not taking statins (31.8% vs. 39.6%, $p = 0.05$). There was a trend for statin use to vary by ARCC site ($p = 0.07$). Compared to those who had not taken antioxidants, those who were or had taken them were higher educated (15.8 ± 3.4 years vs. 14.6 ± 3.9 years, $p = 0.006$), less likely to have a history of diabetes (12.2% vs. 21.4%, $p = 0.026$), and use varied by ARCC site ($p = 0.004$). Of the patients taking antioxidants, 49.6% were diagnosed with Petersen or ADCS criteria as compared to 39.5% of those patients not taking antioxidants ($p = 0.05$). Compared to those who had not taken folic acid, those who were or had taken it were more likely to be male (67.6% vs. 50.7%, $p < 0.05$), have a higher BRDRS score (2.9 ± 3.0 vs. 1.6 ± 2.1 , $p = 0.019$), and differed by site ($p = 0.03$).

Four multivariate logistic regression models showed different patterns for each medication group. Patients were more likely to be taking an anti-AD medication if they were older (odds ratio [OR] 1.26; 95% confidence interval [CI]: 1.01 – 1.57), more highly educated (OR 1.39; 95% CI: 1.06 – 1.82), had greater functional impairment (OR 1.76; 95% CI: 1.38 – 2.24), were an amnestic Rtype (OR 1.83; 95% CI: 1.18 – 2.85), and were not diagnosed according to Petersen or ADCS criteria (OR 0.65; 95% CI: 0.42 – 1.00) (Table 3). Patients were more likely to take statins if they had a history of diabetes (OR 2.40; 95% CI: 1.52 – 3.80), hypertension (OR 2.19; 95% CI: 1.48 – 3.24), or MI (OR 4.34; 95% CI: 2.03 – 9.26), or were male (OR 1.58; 95% CI: 1.10 – 2.27). Patients taking statins were less likely to have mild neurocognitive disorder (OR 0.61; 95% CI: 0.40 – 0.91) (Table 3). Patients were more likely to take antioxidants if they had higher education (OR 1.42; 95% CI: 1.07 – 1.89), did not report a history of diabetes (OR 0.53; 95% CI: 0.29 – 0.98), and there was more site variability for those patients taking antioxidants (OR 1.13; 95% CI: 1.04 – 1.22) (Table 3). Patients were more likely to take folic acid if they reported a non-white race (OR 2.32; 95% CI: 1.01 – 5.31), were male (OR 2.84; 95% CI: 1.26 – 6.42), and had greater functional impairment (OR 1.72; 95% CI: 1.27 – 2.34). None of the models showed evidence for lack of fit or collinearity between variables.

DISCUSSION

This is the first study to systematically explore “real world” pharmacological treatment practices for patients with MCI. We found that one quarter of MCI patients evaluated at ARCCs had or were taking anti-AD medications, almost half had or were taking statins, one-fifth had or were taking antioxidants, and almost one-fifteenth had or were taking folic acid. Different patient characteristics were associated with medication use for each medication group. Anti-AD medication use was highly associated with functional impairment, amnestic subtype, and

education, suggesting that patients who were more functionally impaired and had memory problems were more likely to be on these medications. Interestingly, MMSE score was not associated with anti-AD medication use. Statin use was highly associated with cardiovascular health history and male gender, which is consistent with a primary indication for cardiovascular disease and hyperlipidemia. Antioxidant use was highly associated with education and site. Education, which may reflect differences in socio-economic status, was associated with taking both anti-AD medications and antioxidants, suggesting that more highly educated individuals may have more access to information on the potential benefits of medications and may be able to afford them more easily. In addition, folic acid use was associated with race, gender, and functional status.

Many patients were taking the four medication classes despite their questionable efficacy. While donepezil and other ChIs are beneficial for mild to moderate AD, clinical trials of ChIs have shown little to no improvement of symptoms or delay of progression to AD in MCI patients; although these results are controversial^{16, 20-22}. Memantine improves the cognitive symptoms in moderate to severe AD, but has not been shown to be beneficial for mild AD or MCI²³. While vitamin E and other antioxidants may have beneficial effects on cognition, they are not generally recommended for dementia treatment due to an increased risk of heart failure and mortality^{5, 24}. In addition, vitamin E has not shown any significant benefit for slowing the progression to dementia in MCI patients¹⁶ or improving cognitive function in normal elders²⁵. Statins, specifically lovastatin and pravastatin, have been shown to delay cognitive and functional decline in mild to moderate AD, and may protect against risk of developing AD^{4, 6-8, 26}. However, a review of statin literature found no conclusive evidence for the use of statins in AD⁹. Finally, while increasing folic acid intake reduces homocysteine levels, most randomized, controlled trials indicate that folic acid itself is not sufficient to prevent cognitive decline in people with cognitive impairment²⁷⁻³⁰.

There are several limitations to this study that are important to consider. First, several sub-diagnoses comprised the overall category of MCI, which may make the study population heterogeneous. In addition, the primary indication for medication use is unclear. While it is most likely that anti-AD medications were prescribed to address cognitive symptoms, we cannot determine whether statins, antioxidants, or folic acid were prescribed for MCI or for other conditions. It is unlikely that these three medications were prescribed solely for cognitive decline. The ARCCs are mostly urban, academically affiliated hospitals where patients are seen by specialists. This may make the results less generalizable to patients seen in the community by primary care physicians. A limitation of the MUDS is that documentation is restricted to whether the patient had taken or was taking the medication at the initial evaluation, and not when the medication was prescribed by ARCC physicians.

This study suggests that despite the lack of FDA-approved medications for MCI treatment, a quarter of MCI patients are being treated with “off-label” ChIs and 11% with “off-label” memantine. This study emphasizes the need to develop new MCI treatments, as currently there are only medications of questionable efficacy to treat a common and possibly progressive syndrome. Further investigation on the effect of treatment patterns on the clinical course of MCI is a critical next step.

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Table 1

Frequency of medication use among the 578 patients diagnosed with Mild Cognitive Impairment (MCI).

Medication	All MCI* patients (N = 578)	MCI patients taking anti-AD* medications (N = 166) N (%)
Cholinesterase Inhibitors	103 (17.8)	---
Memantine	21 (3.6)	---
Cholinesterase Inhibitors and Memantine (anti-AD medications)	42 (7.3)	---
Statins	252 (43.6)	77 (46.4)
Antioxidants	115 (19.9)	39 (23.5)
Folic Acid	37 (6.4)	15 (9.0)

*
AD = Alzheimer's Disease

Table 2

Characteristics of 578 Mild Cognitive Impairment (MCI) patients by anti-Alzheimer's Disease medication use group.

Characteristic	On Anti-AD* Medications Mean ($\pm$ sd) * or N (%)	No Anti-AD* Medications	P Value
Age	77.5 (7.2)	74.2 (10.6)	< 0.001
Above HS* Education	125 (75.3%)	297 (72.1%)	0.201
Non-White Race	132 (79.5%)	315 (76.5%)	0.426
Male	93 (56.0%)	203 (49.3%)	0.132
MMSE*	26.1 (2.9)	26.8 (2.7)	0.006
Diabetes	27 (16.3%)	86 (20.9%)	0.206
Hypertension	110 (66.3%)	256 (62.1%)	0.351
Myocardial Infarct	14 (8.4%)	31 (7.5%)	0.712
Stroke/TIA*	24 (14.5%)	51 (12.4%)	0.501
BRDRS*	2.3 (2.2)	1.4 (2.1)	< 0.001
Site	---	---	< 0.001
Amnesic Disorder	59 (35.5%)	95 (23.1%)	0.002
Single Mild Non-Memory Cognitive Impairment	17 (10.2%)	47 (11.4%)	0.679
Mild Neurocognitive Disorder	58 (34.9%)	151 (36.7%)	0.684
MCI* - Petersen or ADCS Criteria	60 (36.1%)	180 (43.7%)	0.091

* AD = Alzheimer's Disease; HS = high school; MMSE = Mini Mental Status Examination (range = 0 – 30 where lower score indicates poorer performance); TIA = transient ischemic attack; BRDRS = Blessed-Roth Dementia Rating Scale (range = 0 – 17 where higher score indicates poorer performance); sd = standard deviation

Table 3

Multivariate models of the likelihood of taking medications among the 578 patients with Mild Cognitive Impairment (MCI).

Characteristic	Anti-AD* Medications	Statins Odds Ratio (95% Confidence Interval)	Antioxidants	Folic Acid
Age	1.26 (1.01 – 1.57)	---	---	---
Education	1.39 (1.06 – 1.82)	---	1.42 (1.07 – 1.89)	1.34 (0.83 – 2.16)
Non-White Race	---	---	---	2.32 (1.01 – 5.31)
Male	1.26 (0.84 – 1.89)	1.58 (1.10– 2.27)	---	2.84 (1.26 – 6.42)
MMSE*	0.87 (0.70 – 1.09)	---	---	---
Diabetes	---	2.40 (1.52 – 3.80)	0.53 (0.29 – 0.98)	---
Hypertension	---	2.19 (1.48 – 3.24)	---	---
Myocardial Infarct	---	4.34 (2.03 – 9.26)	---	---
Stroke/TIA*	---	1.25 (0.73 – 2.12)	---	0.31 (0.07 – 1.37)
BRDRS*	1.76 (1.38 – 2.24)	---	---	1.72 (1.27 – 2.34)
Site	1.00 (0.93 – 1.09)	0.95 (0.89 – 1.02)	1.13 (1.04 – 1.22)	1.04 (0.91 – 1.20)
Amnesic Disorder	1.83 (1.18 – 2.85)	1.08 (0.70 – 1.67)	---	0.68 (0.26 – 1.75)
Mild Neurocognitive Disorder	---	0.61 (0.40 – 0.91)	0.75 (0.46 – 1.24)	---
MCI* - Petersen or ADCS Criteria	0.65 (0.42 – 1.00)	---	1.01 (0.62 – 1.63)	---

* AD = Alzheimer's Disease; MMSE = Mini Mental Status Examination (range = 0 – 30 where lower score indicates poorer performance); TIA = transient ischemic attack; BRDRS = Blessed-Roth Dementia Rating Scale (range = 0 – 17 where higher score indicates poorer performance)