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Cholinesterase Inhibitor and Memantine Use in Newly Admitted Nursing Home Residents with Dementia

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Abstract

OBJECTIVES—To quantify the use of cholinesterase inhibitors (ChEIs) and memantine in nursing home (NH) residents with dementia upon NH admission and 3 months later and to examine factors associated with reduction in therapy.

DESIGN—Retrospective cohort study.

SETTING—Nationwide sample of U.S. NHs.

PARTICIPANTS—Three thousand five hundred six NH residents with dementia newly admitted in 2006.

MEASUREMENTS—Data from pharmacy dispensing records were used to determine ChEI and memantine medication use upon NH admission and at 3-month follow-up. The Minimum Data Set was used to determine resident- and facility-level characteristics. Severity of dementia was defined using the Cognitive Performance Scale (CPS).

RESULTS—Overall, 40.1% (n = 1,407) of newly admitted NH residents with dementia received ChEIs and memantine on NH admission. Use of ChEIs and memantine on admission was significantly greater in residents with mild to moderately severe dementia (41.2%) than in those with advanced dementia (33.3%, $P = .001$). After 3 months, ChEI and memantine use decreased by about half in both groups (48.6% with mild to moderately severe dementia vs 57.0% with advanced dementia, $P < .05$). NH residents with advanced dementia were significantly more likely

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Author Contributions: Tjia and Briesacher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tjia, Givens. Acquisition of data: Briesacher. Analysis and interpretation of data: Parsons, Briesacher, Givens, Chen, Tjia. Drafting of manuscript: Parsons, Tjia. Critical revision of manuscript for important intellectual content: Parsons, Briesacher, Givens, Chen, Tjia. Statistical analysis: Parsons, Givens, Briesacher, Tjia. Obtained funding: Tjia. Study supervision: Tjia.

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reduce their use of ChEIs and memantine than those with mild to moderately severe dementia (odds ratio =1.44, 95% confidence interval =1.03–2.01, $P=.04$).

CONCLUSION—Many NH residents with advanced dementia receive ChEIs and memantine upon NH admission, and approximately half of these decrease their medication use over the ensuing months. Further study is required to optimize use of ChEIs and memantine in NH populations and to determine the effects of withdrawing therapy on resident outcomes.

Keywords

dementia; nursing homes; cholinesterase inhibitor; memantine

Dementia is a progressive neurodegenerative disorder that is currently estimated to affect 4.4 million people in North America.¹ Two classes of drugs prescribed to relieve symptoms of memory loss and to forestall the progression of cognitive, behavioral, and functional declines are cholinesterase inhibitors (ChEIs) and memantine.² In the United States, ChEIs, which include donepezil, galantamine, rivastigmine, and tacrine, have Food and Drug Administration (FDA) approval for mild to moderate dementia of the Alzheimer's type, and donepezil has FDA approval for more-advanced disease.² The FDA has approved memantine, an agonist-antagonist (partial agonist and uncompetitive antagonist) of the *N*-methyl-D-aspartic acid (NMDA) receptor, for the treatment of moderate to severe Alzheimer's disease.^{2,3}

Despite pharmacological treatment, individuals with dementia progress to advanced disease, which is characterized by an inability to communicate and recognize family, difficulty eating and swallowing, and dependence in all activities of daily living (ADLs).⁴ These individuals have a prognosis comparable with that of metastatic breast cancer or stage IV heart failure,⁵ and at this stage of illness, although families may desire symptom management, the usefulness of ChEIs and memantine is unclear.^{6,7} Furthermore, the majority of families of individuals with advanced dementia endorse comfort as the primary goal of treatment,⁵ and a recent consensus panel considered ChEIs to be never appropriate for individuals with advanced dementia when comfort is the goal of care.⁷

There are several reasons for controversy surrounding the use of ChEIs and memantine in individuals with advanced disease. First, despite some evidence that donepezil, alone and in combination with memantine, improves cognitive, functional, and behavioral indicators in individuals with moderate or advanced disease,^{8–18} experts argue that the relevance of small point differences between drug- and placebo-treated individuals on quantitative scales do not translate into clinically meaningful outcomes.¹⁹ Second, some experts question the usefulness of ChEIs and memantine in the nursing home (NH) setting, particularly in light of the cost of the drugs,²⁰ because the outcome for many initial trials was NH placement.¹⁹ Third, many trials have been conducted in the community setting, yet the results are extrapolated to individuals in the NH setting who are more functionally impaired.

Despite pressure to reduce overhead cost in long-term care, little is known about the use of ChEIs and memantine in this setting. Therefore, this study was conducted using a nationwide sample of NH residents in the United States, to compare ChEI and memantine

use in residents with advanced dementia with that in residents with mild to moderately severe dementia upon NH admission and 3 months after admission and to examine resident-level characteristics associated with reduction of ChEI and medication use during the 3 months after NH admission. A secondary aim was to evaluate whether hospice use, feeding tube use, or orders to limit procedures or hospital transfer were associated with use of ChEIs and memantine in NH residents with dementia.

METHODS

Study Design

Data were obtained from Omnicare, Inc., a provider of pharmaceutical care that serves approximately 720,000 residents in 9,800 NHs located throughout the United States. The Omnicare research database is a nationwide sample that includes more than 50% of NHs from all 50 states in the United States and contains a geographic distribution similar to that of NH residents in the December 2006 Centers for Medicare and Medicaid Services (CMS) Online Survey Certification and Reporting (OSCAR) Data (Northeast, 24% vs 23%; Midwest, 36% vs 29%; South, 28% vs 34%; and West, 11% vs 14%).²¹ It contains pharmacy dispensing data for residents and information regarding pharmacy claims linked to resident-level assessments from the Minimum Data Set (MDS) 2.0 of the Resident Assessment Instrument. The pharmacy data are linkable to a subset of approximately 66,000 residents with MDS data in 2006; these are residents who live in facilities with enhanced service contracts with Omnicare to complete MDS assessments and represent approximately 15% of the total Omnicare population. These data have been previously used to examine prescribing of antipsychotics to NH residents.²² The MDS is a standardized, clinically based instrument used in NHs in the United States to assess resident condition for clinical and reimbursement purposes. It collects information on the demographic, functional, medical, psychological, and cognitive status of residents.^{23,24} CMS requires that each certified facility conduct a MDS assessment of all residents on admission, quarterly thereafter, and with significant changes in clinical status.

Study Sample

The sampling frame for this study was 12,720 NH long-stay residents with a full MDS assessment and newly admitted in 2006. Long-stay residents were defined as individuals having a NH stay of longer than 3 consecutive months. Short-stay residents were excluded because previous research has shown significant differences between long- and short-stay NH residents with respect to burden of illness and functional status.²⁵

Residents with a diagnosis of dementia were identified using Section 1 of the MDS. Because Alzheimer's disease is underdocumented in the MDS, residents classified as having dementia of the Alzheimer's type and dementia other than Alzheimer's type on admission were included. Residents who did not have associated prescription medication files and those living in NHs with fewer than five residents were excluded. Of the 4,080 residents meeting these criteria, 85.9% had a follow-up quarterly assessment, resulting in a final sample of 3,506 residents.

Use of ChEIs and Memantine

Medication use was assessed on admission and at the first quarterly MDS assessment. ChEI and memantine use, including use of any ChEI (donepezil, rivastigmine, or galantamine) or memantine, was identified using pharmacy dispensing data for these drugs within 14 days of the admission and quarterly assessments. Monotherapy was defined as evidence of dispensing of any single ChEI or memantine within 14 days of the assessment, and combination therapy was defined as evidence of dispensing of more than one ChEI or dispensing of a ChEI and memantine within 14 days of the assessment. Tacrine was omitted because it was not used in the sample.

Resident- and Facility-Level Characteristics

Resident characteristics were obtained from the MDS admission assessment. Demographic information included age, sex, race and ethnicity, marital status, region of residence (Midwest, Northeast, South, West), and whether residents were being cared for in a specialized dementia care unit. The MDS Changes in Health, End-stage disease and Symptoms and Signs (CHESS) score, which provides a measure of resident frailty ranging from 0 (no frailty) to 5 (high frailty),²⁶ was calculated for each resident on admission. The Behavioral Index was used to categorize behavioral problems in residents. This index is based on the frequency and number of behaviors such as wandering, being verbally or physically abusive and socially inappropriate, and has been previously utilized in research.^{27–30} Ranging from 0 to 2, 0 or 1 corresponds to normal to mild behavioral problems and 2 to moderate to severe behavioral problems. Cognitive function was assessed using the Cognitive Performance Scale (CPS), which categorizes impairment into minimal (0–1), moderate (2–3), and severe (4–6)³¹ and has demonstrated good correlation with the Mini-Mental State Examination (MMSE).^{31,32} Residents with CPS scores of 0 to 4 were classified as having mild to moderately severe dementia. Advanced dementia was defined as a CPS score of 5 or 6 (also called severe to very severe dementia on the CPS scale). Do-not-resuscitate (DNR) and do-not-hospitalize (DNH) orders, use of hospice services, and the presence of a feeding tube were measured at the 3-month quarterly assessment. NH characteristics included the number of long-stay residents and geographic location of the NH as categorized according to U.S. Census region.

Statistical Analysis

Descriptive statistics were used to examine the prevalence of ChEI and memantine use at admission and 3 months after admission according to severity of dementia. The chi-square test was used to test for significance of differences in use of ChEIs and memantine between residents with advanced dementia and those with mild to moderately severe dementia. Multivariable logistic regression was conducted to examine independent factors associated with reduction in ChEI and memantine use 3 months after admission. Because observations within NHs are correlated, analyses were clustered according to NH facility. Variables with $P < .2$ in unadjusted analysis were included in the multivariate analysis, with statistical significance set at $P < .05$. The final multivariable model included age, sex, race (white vs nonwhite), region (Midwest vs Northeast, Midwest vs South, Midwest vs West), whether the resident was being cared for in a dementia unit, type of dementia (Alzheimer's type of

dementia vs dementia other than Alzheimer's type), severity of dementia (advanced vs mild to moderately severe), Behavioral Index, CHES score, DNH and DNR orders, and use of hospice services or a feeding tube at 3-month follow-up. Adjusted odds ratios for reducing ChEIs and memantine were estimated. STATA version 10.0 software (StataCorp, College Station, TX) was used to conduct all statistical analyses. The institutional review board of the University of Massachusetts Medical School exempted this research from review.

RESULTS

Sample Characteristics

Of the 3,506 residents in the sample, 475 (13.5%) met criteria for advanced dementia (Table 1). The mean age for the overall sample was 81.6, and the majority were female and white and had a diagnosis of dementia other than the Alzheimer's type. Overall, 10.3% lived on a dementia unit, 27.3% had some behavioral issue, and 42.8% had a DNR order. Of residents with advanced dementia, 13.9% lived on a dementia unit, 36.6% had some behavioral issue, and 47.6% had a DNR order.

Prevalence of ChEI and Memantine Use on Admission

Overall, 40.1% of the population ($n = 1,407$) received ChEIs and memantine on NH admission. Use of ChEIs and memantine on admission was significantly higher in residents with mild to moderately severe dementia than in those with advanced dementia (41.2% vs 33.3%, $P = .001$) (Table 2). Monotherapy with ChEIs or memantine was more common than combination therapy on NH admission, regardless of severity of dementia (Table 2). A total of 1,034 NH residents (29.5%) received monotherapy on admission, and 373 (10.6%) received combination therapy. Treatment on admission with monotherapy or combination therapy was more common in residents with mild to moderately severe dementia than those with advanced dementia (30.4% vs 23.8% and 10.8% vs 9.5%, respectively).

Donepezil was the most common of the ChEI and memantine monotherapies taken on NH admission, taken by a total of 68.5% of residents with mild to moderately severe dementia and residents with advanced dementia combined. Memantine was the next most commonly used medication, taken by 20.0% of all residents with dementia receiving monotherapy on admission. Memantine and donepezil was the most common combination therapy, used by 74.5% of residents prescribed combination therapy.

Prevalence of ChEI and Memantine Use at 3 Months

Table 2 illustrates the change in ChEI and memantine use between admission and first quarterly MDS assessment. After 3 months of follow-up, use of ChEIs and memantine decreased significantly, to approximately one-quarter in both groups (31.1% mild to moderately severe dementia vs 25.6% advanced dementia, $P = .01$), and decreases occurred in monotherapy and combination therapies. Table 3 shows how many residents continued therapy from admission to 3-month follow-up and how many experienced a reduction in therapy. Continued therapy included having no change or intensification from monotherapy to combination therapy.

Residents with advanced dementia were significantly more likely than those with mild to moderately severe dementia to experience a reduction in ChEI and memantine use within 3 months of NH admission (Table 3). Almost half (48.6%) of residents with mild to moderately severe dementia had a reduction in monotherapy or combination ChEI and memantine drug therapy compared with over half (57.0%) of residents with advanced dementia ($P<.05$).

Multivariable Analysis of Correlates of Reduction in ChEI and Memantine Use After NH Admission

Severity of dementia was the only factor found to be significantly associated with reduction of ChEI and memantine use within 3 months of follow-up, after controlling for other potential confounders (odds ratio =1.44, 95% confidence interval =1.03–2.01, $P=.04$) (Table 4). Race and geographic region of NH were not associated with reduction in ChEI and memantine use. Furthermore, reduction in ChEI and memantine use after NH admission was not associated with DNR order, DNH order, feeding tube, or hospice enrollment (Table 4).

DISCUSSION

This study builds on the growing pharmacoepidemiological literature regarding ChEIs^{33–38} and memantine^{39,40} by quantifying their use in the understudied population of NH residents with advanced dementia. It found that 33% of residents with advanced dementia were prescribed ChEIs or memantine upon admission to the NH. In the 3 months after admission, 57% of residents with advanced dementia experienced a discontinuation of their ChEI, memantine, or both. At 3 months, one-quarter of residents with advanced dementia continued on a ChEI or memantine. There was no evidence that DNR or DNH orders, tube feeding, or hospice enrollment was associated with reducing intensity of ChEI and memantine use.

Optimizing the use of drugs to treat dementia is challenging, and the continuation of these medications beyond their benefit and initial indication is problematic for several reasons. First, the continued use of medications beyond the presence of a clear indication contributes to polypharmacy, which can contribute to anorexia and increases the risk of adverse drug events.⁴¹ Second, ChEI use can lead to a prescribing cascade related to their effects on the autonomic nervous system by precipitating urge urinary incontinence. A prescribing cascade is an adverse reaction to one drug resulting in the prescribing of a potentially inappropriate second drug.⁴² A large, population-based study of individuals with dementia found that those taking a ChEI had a hazard ratio of 1.55 for being prescribed an anticholinergic drug for urinary incontinence.⁴³ Third, potentially unnecessary use of ChEIs and memantine contributes to greater spending for pharmaceutical care at the individual and societal level. Spending for drugs in NHs represents a significant burden to healthcare payers such as Medicare and Medicaid. Fourth, administration of questionably beneficial medications can represent an unnecessary burden to people with dementia, who often have difficulty eating and swallowing^{44,45} and for whom the goal of care is typically comfort.⁵

Continued use of ChEIs and memantine in NH residents with dementia may contribute to adverse effects in the absence of clear benefit, although discontinuation may also pose risks.

One retrospective analysis found discontinuation of ChEIs in NH residents with more-severe dementia may be associated with adverse behavioral changes, increasing severity of aggressive behaviors, and decreased time spent engaging in leisure-related activities.³⁶ Another survey of U.S. hospice medical directors reported that many observed accelerated cognitive and functional decline or emergence of challenging behaviors after the discontinuation of ChEIs or memantine.⁴⁶ A second challenge to discontinuation is that families of residents with dementia are often reluctant to discontinue medications, because such discontinuation may symbolize abandonment and signal the progression to terminal illness.⁴⁷ Finally, there are few clear, well-accepted, evidence-based guidelines about discontinuation of medications in individuals with advanced dementia.

Given these concerns, it was not surprising to find that one-third of residents with dementia were prescribed ChEIs and memantine upon admission and that approximately one-quarter continue after 3 months. These numbers are consistent with other studies in long-term care^{17,48} and hospice⁴⁹ settings reporting that many individuals die while receiving ChEIs.

The only factor found to be associated with ChEI or memantine discontinuation was having advanced dementia, probably because the greatest controversy for use centers on this particular subgroup of people with dementia. Although the FDA-approved indications for donepezil and memantine include moderate to severe dementia, their clinical efficacy in end-stage disease remains an issue of debate.^{6,11,49} The majority of hospice medical directors in a U.S.-based survey did not consider ChEIs or memantine to be effective in persons with advanced dementia and recommended discontinuing these therapies to families at the time of hospice admission.⁴⁶ Furthermore, there is no convincing evidence for efficacy of memantine in end-stage disease. Unfortunately, treatment guidelines provide physicians with little guidance on how to determine benefit, how long to treat, and under what conditions to discontinue these medications.¹¹

This study was subject to some limitations. First, the data come from a single long-term care pharmacy provider with a large nationwide sample. Caution is recommended in generalizing these results to all NH residents in the United States. Second, NHs with fewer than five residents were excluded because their ChEI and memantine rates were unstable owing to the small number of residents. Limiting the study sample therefore prevents the interpretation of these findings to be extended to smaller facilities. Third, at approximately 44%, the prevalence of dementia was slightly lower than the 50% prevalence rate in the U.S. NH population reported by other studies.^{35,37,50} This may be because of uncertainties in diagnosis that may result in some residents with Alzheimer's disease being diagnosed with dementia of the non-Alzheimer's type. Diagnostic misclassification is an inherent limitation of the MDS,³¹ and diagnostic heterogeneity is an important unmeasured confounder in this study. It has also been recognized as a limitation of other studies involving NH residents with dementia.³⁶ However, the current results are still meaningful because they indicate how NH residents diagnosed with Alzheimer's disease or with dementia of the non-Alzheimer's type are managed medically. Although regulatory approval specifies the use of ChEIs and memantine for Alzheimer's disease, in clinical practice, they are also prescribed for the other dementias.² Fourth, the MDS itself has limitations, and because of data limitation, potentially important facility-level characteristics, such as location of the NHs (rural vs

urban) and staffing, which may affect prescribing of ChEIs and memantine in NHs, may not have been measured.

CONCLUSION

This study indicates that, although there is a significant decrease in ChEI and memantine use 3 months after NH admission, a large number of residents with advanced dementia remain treated with ChEIs and memantine despite the questionable efficacy of these treatments in advanced illness. Further study is needed of people with advanced dementia to better understand the clinical outcomes of discontinuing therapy, including changes in quality of life and overall survival.

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Table 1

Characteristics of Nursing Home (NH) Residents with Dementia Who Had a 3-Month Follow-Up Assessment, According to Use of Cholinesterase Inhibitors and Memantine

Characteristic	Overall N =3,506	Dementia Severity on Admission	
		Mild to Moderately Severe [*] n =3,031	Advanced [†] n =475
Age, mean $\pm$ standard deviation	81.6 $\pm$ 9.1	81.8 $\pm$ 9.1	80.6 $\pm$ 9.2
Female, n (%)	2,420 (69.1)	2,083 (68.7)	337 (71.0)
Race, n (%)			
White	2,727 (77.8)	2,360 (77.9)	367 (77.3)
Black	504 (14.4)	427 (14.1)	77 (16.2)
Hispanic	191 (5.5)	170 (5.6)	21 (4.4)
Other	84 (2.4)	74 (2.4)	10 (2.1)
Region of residence, n (%)			
Midwest	944 (26.9)	818 (27.0)	126 (26.5)
Northeast	415 (11.8)	365 (12.0)	50 (10.5)
South	1,584 (45.2)	1,376 (45.4)	208 (43.8)
West	558 (15.9)	467 (15.4)	91 (19.2)
Missing	5 (0.1)	5 (0.2)	0 (0)
Dementia unit, n (%)	362 (10.3)	296 (9.8)	66 (13.9)
Type of dementia, n (%)			
Other than Alzheimer's type	2,428 (69.2)	2,153 (71.0)	275 (57.9)
Alzheimer's type	1,078 (30.8)	878 (29.0)	200 (42.1)
Behavioral Index [‡] on admission			
0 (none)	2,550 (72.7)	2,249 (74.2)	301 (63.4)
1 (minor)	905 (25.8)	743 (24.5)	162 (34.1)
2 (severe)	51 (1.5)	39 (1.3)	12 (2.5)
Changes in Health, End-stage disease and Symptoms and Signs score on admission [§]			
0	775 (22.1)	674 (22.2)	101 (21.3)
1	1,094 (31.2)	936 (30.9)	158 (33.3)
2	971 (27.7)	841 (27.8)	130 (27.4)
3–5	666 (19.0)	580 (19.1)	86 (18.1)
Do-not-resuscitate order	1,501 (42.8)	1,275 (42.1)	226 (47.6)
Do-not-hospitalize order	78 (2.3)	63 (2.1)	15 (3.4)
Hospice services	72 (2.1)	50 (1.7)	22 (4.6)
Feeding tube	238 (7.8)	143 (4.7)	95 (20.0)

Cognitive Performance Score of

^{*} 1–4 or

[†] 5–6.

[‡] Severity of behavioral problems ranging from 0 (normal) to 1 (mild behavioral problems) to 2 (moderate to severe behavioral problems).

[§]A measure of frailty ranging from 0 (no frailty) to 5 (high frailty).

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Table 2

Type of Cholinesterase Inhibitor and Memantine According to Severity of Dementia on Admission and at 3 Months

Type of Therapy	Mild to Moderately Severe		Advanced	
	Admission n =3,031	3 Months n =3,025	Admission n =475	3 Months n =481
Any therapy (%)	1,249 (41.2)	940 (31.1)	158 (33.3)	123 (25.6)
Monotherapy	921 (30.4)	754 (24.9)	113 (23.8)	100 (20.8)
Donepezil	644 (21.3)	464 (15.3)	65 (13.7)	52 (10.8)
Memantine	174 (5.7)	205 (6.8)	33 (7.0)	37 (7.7)
Rivastigmine	47 (1.5)	47 (1.6)	8 (1.7)	5 (1.0)
Galantamine	56 (1.9)	38 (1.3)	7 (1.5)	6 (1.3)
Combination therapy (%)	328 (10.8)	186 (6.2)	45 (9.5)	23 (4.8)
Memantine and donepezil	246 (8.1)	148 (4.9)	32 (6.7)	19 (4.0)
Memantine and rivastigmine	41 (1.4)	19 (0.6)	5 (1.1)	1 (0.2)
Memantine and galantamine	37 (1.2)	17 (0.6)	7 (1.5)	3 (0.6)
Donepezil and galantamine	2 (0.1)	0 (0.0)	1 (0.2)	0 (0)
Donepezil and rivastigmine	0 (0)	2 (0.1)	0 (0)	0 (0)
Donepezil, galantamine, and memantine	2 (0.1)	0 (0)	0 (0)	0 (0)

Table 3

Course of Cholinesterase Inhibitor and Memantine Use over 3 Months in Residents on Therapy at NH Admission (n =1,407) According to Severity of Dementia

Therapy at Admission	n (%)	
	Continued or Intensified	Reduction in Therapy*
Mild to moderately severe dementia		
Monotherapy (n =921)	506 (54.9)	415 (45.1)
Combination (n =328)	136 (41.6)	192 (58.5)
Total (n =1,249)	642 (41.5)	607 (48.6)
Advanced dementia		
Monotherapy (n =113)	56 (49.6)	57 (50.4)
Combination (n =45)	12 (26.7)	33 (73.3)
Total (n =158)	68 (43.0)	90 (57.0)

* Includes combination therapy to combination with fewer medications, monotherapy or no therapy, and monotherapy to no therapy.

Table 4

Factors Associated with Reduction in Cholinesterase Inhibitor and Memantine Use* at 3 Months (n=1,407)

Factor	Unadjusted	Adjusted
	Odds Ratio (95% Confidence Interval)	
Age	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Female	0.95 (0.76–1.20)	0.95 (0.76–1.20)
Race (vs white)		
Black	1.24 [†] (0.91–1.70)	1.17 (0.85–1.61)
Hispanic	0.94 (0.89–1.51)	0.96 (0.60–1.56)
Other	1.22 (0.56–2.67)	1.27 (0.58–2.80)
Advanced dementia (vs mild to moderately severe)	1.40 [†] (1.00–1.95)	1.44 [‡] (1.03–2.01)
Region (vs Midwest)		
Northeast	1.03 (0.72–1.46)	1.05 (0.74–1.50)
South	0.95 (0.74–1.22)	0.92 (0.72–1.19)
West	0.74 [†] (0.52–1.06)	0.73 (0.51–1.05)
Dementia unit at 3 months	1.13 (0.82–1.57)	
Alzheimer's type of dementia (vs dementia other than Alzheimer's)	1.12 (0.91–1.39)	
Behavioral Index [§] (vs no behavioral problems)		
Mild behavioral problems	0.99 (0.79–1.25)	
Severe behavioral problems	1.36 (0.57–3.26)	
Changes in Health, End-stage disease and Symptoms and Signs score [¶] (vs 0)		
1	1.02 (0.76–1.35)	
2	0.93 (0.69–1.25)	
3–5	1.01 (0.73–1.40)	
Do-not-resuscitate order	0.82 [†] (0.66–1.01)	0.83 (0.67–1.04)
Do-not-hospitalize order	1.23 (0.53–2.86)	
Hospice services at 3 months	1.56 (0.66–3.68)	
Feeding tube at 3 months	1.26 (0.74–2.14)	

* Reduction from monotherapy to no therapy, or reduction from combination therapy to combination with fewer medications, monotherapy or no therapy. $P < ^{†} .20$, $^{‡} .05$.

[§] Severity of behavioral problems (range 0 (normal) to 1 (mild behavioral problems) to 2 (moderate to severe behavioral problems)).

[¶] A measure of frailty ranging from 0 (no frailty) to 5 (high frailty).