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Brief Report

Cholinesterase Inhibitor and N-Methyl-D-Aspartic Acid Receptor Antagonist Use in Older Adults with End-Stage Dementia: A Survey of Hospice Medical Directors

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Abstract

Background: Cholinesterase inhibitors and N-methyl-D-aspartic acid (NMDA) receptor antagonists are Food and Drug Administration (FDA) approved for the treatment of moderate to severe Alzheimer's disease. As dementia progresses to the end stage and patients become hospice-eligible, clinicians consider whether or not to continue these therapies without the benefit of scientific evidence. We sought to describe hospice medical directors practice patterns and experiences in the use and discontinuation of cholinesterase inhibitors and NMDA receptor antagonists in hospice patients that meet the Medicare hospice criteria for dementia.

Study Design: Mail survey of hospice medical directors from a random sample from the National Hospice and Palliative Care Organization.

Results: Of the 413 eligible participants, 152 completed surveys were returned, yielding a response rate of 37%. Of the respondents, 75% and 33% reported that at least 20% of their patients were taking a cholinesterase inhibitor or memantine, respectively, at the time of hospice admission. The majority of respondents do not consider these therapies effective in persons with end-stage dementia, however, a subset believe that these medications improved patient outcomes including stabilization of cognition (22%), decrease in challenging behaviors (28%), and maintenance of patient function (22%) as well as caregiver outcomes namely reduced caregiver burden (20%) and improved caregiver quality of life (20%). While 80% of respondents recommended discontinuing these therapies to families at the time of hospice enrollment, 72% of respondents reported that families experienced difficulty stopping these therapies. A subset of respondents observed accelerated cognitive (30%) and functional decline (26%) or emergence of challenging behaviors (32%) with medication discontinuation.

Conclusions: The findings from this survey indicate that cholinesterase inhibitors and/or NMDA receptor antagonists are prescribed for a subset of patients with advanced dementia and that a proportion of hospice medical directors report clinical benefit from the ongoing use of these agents. In addition, physician preferences for discontinuing these therapies are frequently at odds with the wishes of family members. Prospective studies are needed to evaluate the clinical impact of the discontinuation of these therapies on patient and caregiver outcomes.

Introduction

As dementia progresses to the advanced stages, goals of treatment frequently shift from curative and/or disease modifying to the alleviation of physical and/or psychological symptoms. Consequently, care providers may recommend discontinuing pharmacologic or other therapies that are not primarily indicated for symptomatic relief.[1] Cholinesterase inhibitors and/or N-methyl-D-aspartate (NMDA) receptor antagonists are prescribed to some persons with end-stage dementia.[2] Randomized double-blinded placebo controlled trials found the cholinesterase inhibitor donepezil and the NMDA receptor antagonist memantine lead to statistically significant beneficial cognitive, functional, and behavioral

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outcomes compared to placebo among persons with moderate to severe Alzheimer's disease.[3–6] However, existing trials lack quality of life and other clinically meaningful indicators and have not examined the efficacy of these therapies in persons with end-stage dementia.[7]

Given the lack of empiric evidence for the use of these therapies in advanced populations, we wanted to better understand the clinical experience and practice patterns of hospice medical directors surrounding the use and discontinuation of cholinesterase inhibitors and NMDA receptor antagonists in hospice patients that met the Medicare hospice criteria for dementia; hereafter denoted interchangeably as advanced or end-stage dementia. We also sought to establish perceived standards of care and establish a relevant research agenda. A physician survey was conducted to (1) estimate the number of patients who were prescribed these therapies at the time of hospice enrollment; (2) assess the perceived benefits of these therapies in end-stage disease; (3) describe the recommendations respondents make to families regarding the use of these therapies; and (4) assess the observed impact of medication discontinuation on patients and caregivers.

Methods

Survey

A mail survey was developed to better understand the experiences of hospice medical directors regarding the use and discontinuation of cholinesterase inhibitors and/or NMDA receptor antagonists among persons admitted to a hospice program with a primary diagnosis of advanced dementia. Domains of interest were identified through literature review and consensus of the authors. The survey was pilot tested using standard cognitive interviewing methods to refine question wording, order, and applicability to the research questions. The survey was divided into two sections: multiple-choice questions regarding donepezil and memantine use subsequent to a hypothetical clinical vignette depicting an older adult with end-stage dementia and questions that quantified respondents' experience in caring for these patients as well as their personal and professional characteristics.

Mailings

A random sample of 500 hospice sites in the United States was obtained in 2007 from the National Hospice and Palliative Care Organization. Mailings were sent to hospice sites addressed to an individual or if unavailable, to the "medical director." Each hospice medical director was assigned an anonymous unique identification number. The first mailing occurred in April 2007 and contained the survey booklet, a stamped preaddressed return envelope, and a cover letter describing the purpose of the study. This mailing was followed by two subsequent mailings to non-responders. The study was approved by Northwestern University's Institutional Review Board.

Statistical analysis

Respondent demographic variables and self-reported clinical experience in caring for persons with end-stage dementia were summarized using descriptive statistics. Unless otherwise noted, we collapsed four point Likert response categories ("definitely yes, probably yes, probably no, definitely no") into dichotomous categories ("yes/no") to facilitate interpretation and analysis. Associations between the likelihood of survey response and participant characteristics were tested by χ^2 analysis. Comparisons analyzing whether or not a physician would recommend medication discontinuation based upon reported clinical benefit of cholinesterase inhibitors and NMDA receptor antagonists use were tested by χ^2 analysis. Statistical analyses were performed using SPSS version 15.01 (SPSS Inc., Chicago, IL).

Results

Of the 500 mailed surveys, 79 were returned by the post office as undeliverable and 8 physicians no longer cared for hospice patients. Of the net sample of 413 possible participants 152 were returned and completed, yielding a response rate of 37%. To assess nonresponder bias, we examined whether participant response varied by gender ($p = 0.63$) or by geographic region ($p = 0.64$).

Characteristics of the 152 respondents and their affiliated hospices are displayed in Table 1. The mean age of respondents was 53.4 years and the majority was male (70%) and Caucasian, non-Hispanic (91%). Seventy-three percent of respondents were employed by moderate-sized hospice programs that were not for profit. Respondents reported that on average, 21% of hospice enrollees in their program had a primary diagnosis of dementia, 50% of whom reside in a long-term care facility.

Table 2 displays respondent self-report of cholinesterase inhibitor and NMDA receptor antagonist use among advanced dementia patients, as well as recommendations made to families regarding whether to discontinue these therapies. Seventy-three percent and 33% of respondents reported more than 20% of their patients on cholinesterase inhibitors and NMDA receptor antagonists, respectively. Approximately 80% of respondents would recommend the discontinuation of these agents as part of the hospice plan of care. However, respondents also reported that 72% of families had difficulty stopping these therapies. Respondents reported that 48% and 47% of their patients actually discontinued cholinesterase inhibitor and NMDA receptor antagonist therapy, respectively.

Table 3 displays physician observations on the perceived effectiveness of cholinesterase inhibitors and NMDA receptor antagonists in patients with end-stage dementia. The reported clinical benefits of cholinesterase inhibitor use include stabilization of cognition (22%), decrease in challenging behaviors (28%), and maintenance of patient function (22%) as well as reduced caregiver burden (20%) and improved caregiver quality of life (20%); similar results were reported with the NMDA receptor antagonist memantine. Respondents indicated that they were significantly less likely to recommend discontinuing cholinesterase inhibitor or NMDA receptor antagonists, if they believed that these therapies stabilized cognition ($p < 0.01$), decreased challenging behaviors ($p < 0.01$), or helped to maintain patient function ($p < 0.01$).

Table 4 displays respondent beliefs related to the potential effects of discontinuing cholinesterase inhibitor and NMDA receptor antagonists, independent of the natural progression of dementia, in persons with end-stage dementia. Some respondents reported that donepezil (or memantine) discontinuation results in accelerated cognitive decline (30%), functional decline (26%), and the emergence of challenging

Table 1. Physician Respondent Characteristics, $N = 152$

Characteristic	*Value*
Age, mean (SD)	53.4 (9.9)
Gender, *n* (%)	
Male	106 (70)
Race/ethnicity, *n* (%)	
Caucasian, non-Hispanic	139 (91)
African American	5 (3)
Hispanic	3 (2)
Others	5 (3)
Years in practice as hospice physician, mean (SD)	11.6 (8)
Medical specialty, *n* (%)	
Primary care	114 (75)
Geriatrics	21 (14)
Oncology/Hematology	11 (7)
Other	6 (4)
Certification from American Board of Hospice and Palliative Medicine, *n* (%)	74 (49)
Characteristics of hospice program where respondents practice	
Average daily census, mean	127
Hospice not for profit, *n* (%)	111 (73)
Affiliated with university, *n* (%)	6 (4)
Experience with end stage dementia	
Patients in doctor's hospice with a primary dementia diagnosis, *n* (%)	32 (21)
Percent of hospice dementia patients residing in long-term care facility, *n* (%)	76 (50)
Doctor reported reading recent literature on donepezil or memantine, *n* (%)	125 (82)

SD, Standard deviation.

behaviors (32%), as well as withdrawal from family activities (25%) and decreased time awake (22%).

Discussion

This study corroborates that a number of patients with a end-stage dementia are prescribed a cholinesterase inhibitor and/or memantine at the time of hospice enrollment.[2,8,9] Approximately 20%–30% of the sampled hospice medical directors described cognitive, behavioral, and/or functional benefits from the ongoing use of these therapies near the end of life. Hospice medical directors who perceive benefits from these therapies are less likely to recommend their discontinuation. Although the majority of respondents would recommend discontinuing donepezil and memantine at the time of hospice enrollment, respondents also reported that almost three-quarters of families have difficulty stopping these therapies. Approximately a quarter of respondents reported observing cognitive and functional decline, the reemergence of challenging behaviors, and increased caregiver burden after either therapy was discontinued.

Table 2. Physician Report of Donepezil[a] and Memantine Use and Recommendations Made to Families on Whether to Discontinue Therapy for End-Stage Dementia Patients, $N = 152$

	Donepezil % yes	*Memantine % yes*
Percent of their patients on therapy at hospice admission		
0%–10%	12	28
11%–20%	15	38
21%–50%	48	26
51%–100%	25	8
Would recommend to discontinue therapy	81	79
Agree that families having a difficult time stopping therapy	72	72
Percent of patients actually discontinued therapy at hospice admission		
0%–25%	24	29
26%–50%	28	24
51%–75%	23	23
76%–100%	25	24

[a]Includes cholinesterase inhibitors, donepezil, rivastigmine, and galantamine.

Theoretical benefits of these therapies in this population may include maintaining cognitive abilities (recognizing family and caregivers), ameliorating functional decline (swallowing and posture), and diminishing behavioral symptoms. Potential downsides of therapy continuation among those in hospice are ongoing side effects (nausea, diarrhea, and poor appetite for cholinesterase inhibitors), drug–drug interactions, pill burden, considerable financial cost, and competing philosophies of care. Withdrawal studies conducted in less advanced populations has been associated with cognitive decline and the reemergence of challenging behaviors, but the impact of drug discontinuation has not been evaluated in advanced dementia populations.[10–12]

The clinical benefits of cholinesterase inhibitor and NMDA receptor antagonist use in person with dementia are frequently questioned. This point is demonstrated by considering the cognitive changes with donepezil use compared to placebo from a typical randomized double-blinded placebo-controlled trial conducted over a 6-month period.[4] Donepezil

Table 3. Physician Report on the Observed Effectiveness of Donepezil and Memantine Use among Patients with End-Stage Dementia, $N = 152$

	Donepezil[a] *% agree*	*Memantine*[a] *% agree*
Improves patient cognition	10	10
Stabilizes patient cognition	22	23
Decreases patient challenging behaviors	28	25
Helps maintain patient function	22	19
Provides palliation patient symptoms	20	18
Improves patient quality of life	15	17
Improves patient energy	4	6
Improves patient survival	3	3
Delays patient time to nursing home placement	17	13
Reduces time spent caregiving	17	16
Reduces caregiver burden	20	18
Improves caregiver quality of life	20	16
Is the standard of care	17	16

[a]Responses are collapsed from four-point Likert type scales (strongly agree, agree, disagree, strongly disagree) into dichotomous categories.

therapy was associated with a statistically significant 4.5 difference in severe impairment battery scores, a cognitive test of 40 questions with scores ranging from 0–100, compared to placebo. However, the actual clinical benefits of these observed differences remains questionable, especially among those with end-stage dementia because these patients are typically excluded from clinical trials. Taken together, clinicians may rely upon data pertaining to less advanced dementia populations, clinical experience, local opinion leaders, and patient/family preferences when making a determination to recommend continuing or discontinuing these therapies.

Several limitations must be considered when interpreting the results of this study. The survey response rate is 37%, limiting the generalizability of the study results. However, the likelihood of survey response did not vary by respondent gender or geographic location of the hospice suggesting the results are representative of the overall sample population. Also, 37% lies within the average range of physician response rate to mailed surveys published in the medical literature and this study represents the first attempt to describe practice patterns among an understudied population.[13] Respondent's treatment recommendations were based upon their clinical experiences; furthermore, self-reported practices may not reflect real-life experiences. However, respondents reported a similar frequency of cholinesterase inhibitor and NMDA receptor antagonist use compared to recently published estimates in epidemiologic studies of end-stage dementia patients.[2]

The findings from this survey indicate that cholinesterase inhibitors and/or NMDA receptor antagonists are prescribed for a subset of patients with advanced dementia and that a proportion of hospice medical directors report clinical benefit from the ongoing use of these agents. In addition, physician preferences for discontinuing these therapies are frequently at odds with the wishes of family members. Prospective studies are needed to evaluate the clinical impact of the discontinuation of these therapies on patient and caregiver outcomes.

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The abstract detailing the preliminary results of the study were accepted and presented as a poster at the 2009 annual meeting of the American Academy of Hospice and Palliative Medicine.

Author Disclosure Statement

Joseph Shega was employed in part during the study period by Northwestern Memorial Home Hospice Program. Lynn Ellner was employed by Midwest Palliative Care and Hospice Center during a portion of the study period. Denys Lau has no conflicts of interest to report. Terri Maxwell was employed by excelleRx during the study period, which provided financial support for survey and cover letter paper and envelopes as well as survey mailings.

Table 4. Physician Experiences with Discontinuation of Donepezil and Memantine among Persons with End-Stage Dementia, $N = 152$

Observed effect with medication discontinuation	*Donepezil*[a] *% always or sometimes*	*Memantine*[a] *% always or sometimes*
Accelerates patient cognitive decline	30	21
Accelerates patient functional decline	26	23
Emergence of patient challenging behaviors	32	27
Patient withdrawal from family or activities	25	23
Decreases patient time awake	22	18
Decreases patient quality of life	17	22
Increases caregiver burden	22	22

[a]Responses are collapsed from four-point scale (always, sometimes, rarely, and never) into dichotomous categories.

Author Disclosure Statement

No competing financial interests exist.

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