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Neuropsychiatric Symptom Patterns in Hospice-Eligible Nursing Home Residents with Advanced Dementia

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Abstract

Objective—The purpose of this study was to determine whether specific neuropsychiatric symptom patterns could be identified in a cohort of hospice-eligible nursing home residents with advanced dementia.

Methods—Surrogate decision-makers gave informed consent to enroll 123 residents from three nursing homes. All participating residents met criteria for hospice-eligibility and were determined by direct examination at the time of study enrollment to have advanced dementia. Retrospective medical record review was used to collect data on residents' demographics, diagnoses, and the presence of any neuropsychiatric symptoms during the six months prior to study enrollment. Latent class analysis (LCA) was used to classify residents based on neuropsychiatric symptom patterns.

Results—Overall, 85% of residents exhibited one or more neuropsychiatric symptoms. LCA revealed that these individuals could be classified into three groups: one with low symptom frequencies (36%) considered to be the normative class, one characterized by psychotic and agitation or aggression (23%), and a third characterized by withdrawal or lethargy (41%).

Conclusions—These results add to the growing understanding of neuropsychiatric symptom patterns in advanced dementia and have implications for more dimensional classification and treatment approaches.

Keywords

Advanced dementia; neuropsychiatric; latent class analysis (LCA); end-of-life

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Caring for the growing population of individuals with dementia is a challenge for our healthcare system. Approximately 79% of individuals with advanced dementia die in assisted-living facilities, nursing homes, or hospitals.¹ Common reasons for making the decision to move to a nursing home are the severity of cognitive impairment, with the attendant decrease in functional independence, and the presence of neuropsychiatric symptoms.^{2–5}

Across the spectrum of disease severity, a majority of individuals with dementia have one or more behavioral or psychiatric disturbances.^{6–8} Several attempts have been made to characterize the pattern of these neuropsychiatric symptoms of dementia. In a comparison of seven factor analytic studies, Lawlor and Bhriain⁹ identified five common symptom clusters: 1) depression, 2) psychotic (hallucinations, delusions, suspiciousness), 3) aggression (physical or verbal aggression toward others or aggressive resistance), 4) motor or behavioral dysregulation (pacing, aimless walking, handling objects inappropriately, sleep disturbance), and 5) apathy (social or emotional withdrawal). A similar five factor structure was found in nursing home residents with advanced dementia¹⁰, suggesting that these non-cognitive symptom clusters remain stable over the course of the illness.

A factor-structure approach to characterize patterns of illness deals primarily with the measurement of neuropsychiatric symptoms and assumes that the sample is homogenous. This approach does not offer insight into how patients cluster empirically into subpopulations based on their symptom profiles. As standard diagnostic criteria are based on expert opinion rather than empiric studies, it is useful to explore the scientific validity and utility of diagnostic criteria for classifying patients by their observed behavior. Latent class analysis (LCA) is increasingly being used to tease apart clinical heterogeneity in patients with the same clinical diagnosis to identify homogenous subpopulations in psychiatric samples using a mixture modeling approach.^{11–16} This statistical approach allows for two functions: first, to categorize patients into latent classes based on their observed symptoms, and second, to identify symptoms that best distinguish between the classes.¹⁷

Two studies have used LCA to classify individuals with dementia into meaningful symptom profile groups based on similar symptom patterns. Lyketsos et al.¹⁸ examined symptom patterns in a sample of 198 community dwelling and residential individuals diagnosed with Alzheimer's dementia in the Utah Cache County Study. Though their sample consisted of only one type of dementia, it included individuals from all stages of dementia from mild to severe cognitive impairment. Three latent classes best described the symptom patterns: one class with a low symptom prevalence, one with an affective syndrome that included depression, irritability or anxiety, and one with a psychotic pattern that included hallucinations with or without delusions. A second LCA study conducted by Moran et al.¹⁹ examining neuropsychiatric symptom patterns in 240 individuals with very mild to mild Alzheimer's dementia also determined that three classes best described the symptom patterns: one class with a low symptom prevalence, one with an affective syndrome characterized by anxiety and depression, and one characterized by aggressive behavior. Across the two LCA studies, two out of three of the latent classes were similar (low-frequency symptom class and affective symptom class) and one was different (psychotic vs. aggression).

Little is known about the neuropsychiatric symptom patterns in advanced dementia near the end of life, yet these may be a significant, and treatable, source of distress and morbidity.^{20–22} Previously reported findings for a sample of nursing home residents with advanced dementia indicate that 85% of the residents experienced neuropsychiatric symptoms, however the prevalence of individual symptom patterns and treatments were not yet characterized.²³ The specific aims of the present study were to: 1) describe the prevalence of various

neuropsychiatric symptoms among hospice-eligible residents with advanced dementia; and 2) describe sub-groups of these individuals based on patterns of neuropsychiatric symptoms.

METHODS

Participants

A total of 126 residents from three nursing homes in Maryland were enrolled between December 2000 and August 2003 in the Care of Nursing Home Residents with Advanced Dementia (CareAD) study. (See Black et al.²³ for a complete description of the site selection and enrollment process.) Those enrolled represented 44% of the 289 eligible residents. Residents with any type of dementia who either were receiving hospice or palliative care or met existing hospice criteria for dementia²⁴ were eligible for study enrollment. Surrogate decision-makers for residents with estimated life expectancies of six months or less gave written informed consent for enrollment of the subject and themselves. A surrogate decision-maker was defined as the resident's legally authorized representative based on either legal guardianship, durable power of attorney for health care, or Maryland's Health Care Decisions Act, in that order of priority. The study was approved by the Institutional Review Boards of the Johns Hopkins Medical Institutions and the University of Maryland and by the research review committees at the three study sites. Of 126 residents who were originally enrolled in the study, one was withdrawn by the surrogate and two did not meet hospice guidelines and were not receiving hospice or palliative care, leaving a total of 123 residents for inclusion in the final analysis.

Data Collection

After enrollment, data were collected from three sources: surrogate decision-makers, direct assessment of the residents, and a retrospective review of the medical records. Surrogate decision-makers were interviewed to obtain information on residents' demographic characteristics and history of dementia. Residents' cognitive functioning was assessed using the Severe Impairment Rating Scale (SIRS)²⁵, an 11-item instrument designed for use with individuals who are likely to score less than six on the Mini-Mental State Examination (MMSE)²⁶. Inter-rater reliability of the SIRS in this study, based on Pearson correlation tests, ranged from $r = 0.993$ ($p = 0.001$) to $r = 1.0$, ($p < 0.001$).

Information abstracted from the medical records included: residents' demographic characteristics, diagnoses, and any neuropsychiatric symptoms that occurred during the six months prior to enrollment (or since admission if less than six months). Follow-up medical record data, continued to be collected at 3-month intervals for up to a 42-month period, however the only follow-up data used for this report were the number of weeks until death for the 90 residents who died during the study period.

Neuropsychiatric symptoms were identified based on actual descriptors recorded by nursing home staff in residents' medical records. The neuropsychiatric symptoms determined from medical record descriptors are listed in Table 1. The prevalence of each neuropsychiatric symptom during the six-month period was determined based on a dichotomous variable, indicating that the symptom was either present or absent.

Previously published reports from the CareAd study indicate that, in addition to advanced dementia, the resident participants were very ill with multiple comorbidities²³, taking a mean number of 14.6 ($SD = 7.4$) medications²⁷. During the six-month pre-enrollment period, the percentage of residents taking medications aimed at reducing mood, behavior, and psychotic symptoms was 42%, 38%, and 24%, respectively.²⁷ Although all study participants were hospice eligible, 32.5% were actually receiving hospice or palliative care.²³

Analysis

Univariate analyses were used to describe the study participants and their characteristics and the proportion of residents with each neuropsychiatric symptom during the six month period prior to study enrollment. A LCA was applied to answer our research question, using the MPlus statistical program, version 4.1.²⁸ MPlus was programmed to generate four models with 2, 3, 4, or 5 classes each. The fit statistics were then compared to determine the model that best fit the data. Residents were assigned to the latent class where their probability of membership was maximum. For additional information about latent class analysis using binary items, the reader is referred to Hagenaars & McCutcheon.²⁹

All subsequent analyses were based upon the subpopulations or classes identified by the LCA. Class comparisons of SIRS scores, months of retrospective record review, and time until death were examined with analyses of variance. Apart from the LCA, all data were analyzed using SPSS Version 13 (SPSS).³⁰ *P* values <0.05 were considered statistically significant for all analyses.

RESULTS

Demographic and Diagnostic Characteristics of the Sample

Of the total sample of 123 hospice-eligible residents, 55% were female, 84% were white, and 16% were African American. The mean age was 81.5 (*SD* = 7.1) years, and the mean educational level was 11.5 (*SD* = 3.4) years. The four most frequent dementia diagnoses were: Alzheimer's (58%), vascular (11%), mixed Alzheimer's and vascular (12%), and not otherwise specified or other (14%). The resident participants were determined to have advanced dementia based on direct assessment using the SIRS. The scores ranged from 0 to 22, with overall mean of 10.3, median of 11, and mode of 18. Two residents scored 22, the maximum possible SIRS score.

Prevalence of Neuropsychiatric Symptoms

Of the total sample, 85% had one or more neuropsychiatric symptoms. The prevalence was 89% among those diagnosed with Alzheimer's and 77% among those diagnosed with vascular dementia. Table 1 shows that the most frequent neuropsychiatric symptoms were: agitation/aggression (50%), depression (46%), and withdrawal/lethargy (43%). Agitation/aggression and depression were also the most frequent symptoms among those diagnosed with either Alzheimer's or vascular dementia. Because of the low prevalence of hypomania (*n* = 1) and inappropriate touching behaviors (*n* = 3) and the association of delirium (*n* = 8) with serious non-dementia related somatic conditions, these symptoms were not included in the LCA.

Latent Class Analysis (LCA)

The LCA clusters individuals rather than symptoms, and each individual is placed into only one class based on symptom patterns. Using an exploratory approach, four latent class models were estimated. The model fit indices are shown in Table 2. There has been significant progress in using statistical criteria to select the best fitting latent class solution¹⁷, and in this analysis we selected the three class solution based on the following goodness of fit comparisons. Lower values on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) for the 3-class solution indicate improvement over the 2-class solution. The Lo-Mendell-Rubin Test (LRT) *p*-value represents the probability that the data have been generated by the model with one less class. The non-significant LRT *p*-value for the 4-class solution indicates that the 4-class solution is not significantly better than the 3-class solution, and so the 3-class solution should be preferred on the basis of parsimony. The 3-class solution entropy value (0.79) measures the degree to which the latent classes are clearly distinguishable from one

another (the closer to 1.0, the better). Overall, the goodness of fit comparisons indicate that the 3-class model has overall better fit.

Table 3 shows the results from the 3-class analysis of nine dichotomous neuropsychiatric symptom categories. Entries are the probabilities of individuals in a class exhibiting a symptom. Individuals in Class 1, ($n = 44$), do not exhibit any symptom with a high probability. Class 1 can be considered to be the normative or low-frequency symptom group for individuals with advanced dementia. The highest probability for any symptom in Class 1 is for depression and agitation/aggression, with probabilities of 0.28 and 0.18 respectively. Class 2 ($n = 29$) is characterized by individuals with high probabilities of exhibiting agitation/aggression (0.91), psychosis/delusions (0.85), depression (0.70), and refusal/resistance (0.66). Class 3 is characterized by individuals with a high probability of withdrawal or lethargy (0.73).

The latent classes were widely distributed across diagnostic categories for dementia (see Table 4). Of the individuals diagnosed with Alzheimer's disease ($n = 71$), 35% were assigned to latent Class 1 (low-frequency symptoms), 24% to Class 2 (agitated/psychotic), and 41% to Class 3 (withdrawn/lethargic). Because there were relatively few individuals with non-Alzheimer's dementia diagnoses, the class assignments by diagnostic category are less interpretable.

The severity of cognitive impairment (SIRS) score was unavailable for 2 residents in Class 3 (withdrawn/lethargic). The SIRS mean scores for the latent classes were: 10.91 ($SD = 6.2$), 12.0 ($SD = 6.3$), and 8.8 ($SD = 7.1$) for Classes 1, 2, and 3 respectively. One-way analysis of variance (ANOVA) determined that the means were not significantly different ($F[2, 118] = 2.34, p = 0.097$).

The numbers of residents within each of the latent classes having medical records, and therefore medical record reviews, of less than six months were 10 (22.7%) from Class 1, 13 (45%) from Class 2, and 18 (36%) from Class 3. A one-way ANOVA testing for differences between classes in the number of months of retrospective medical record review for Class 1 (mean = 5.40, $SD = 1.25$, range = 1.7, 6), Class 2 (mean = 4.71, $SD = 1.75$, range = .4, 6), and Class 3 (mean = 5.10, $SD = 1.46$, range = .7, 6) suggested no significant differences ($F[2, 120] = 1.915, p = .152$). However Levene's test for homogeneity of variances resulted in a p value of .017, indicating that the ANOVA assumption of equal variances was violated. Because of the unequal variances, a non-parametric Kruskal-Wallis test of equal population medians was also calculated ($\chi^2 = 4.219, df = 1, p = .121$) and the results were in agreement with the ANOVA indicating that the medical record review periods were statistically equivalent.

Though the expected survival of all resident participants was less than six months, the death rates by the end of the data collection period were 75%, 72%, and 72% for Classes 1, 2, and 3, respectively. Of the 90 residents who died during the study, the mean number of weeks from enrollment until death for the three latent classes was 56.7 ($SD = 49.7$), 42.4 ($SD = 39.8$), and 39.0 ($SD = 36.9$), and the differences were not significant ($F[2, 87] = 1.58, p = 0.21$).

DISCUSSION

This study documents a high prevalence of numerous neuropsychiatric symptoms in hospice-eligible nursing home residents with dementia. These data add to the growing understanding of neuropsychiatric symptom patterns in dementia and are the first to describe neuropsychiatric syndromal patterns in advanced dementia near the end of life. Neuropsychiatric syndromes potentially define subgroups of dementia patients for whom specific behavioral and medication treatments might be examined.

The majority (85%) of these nursing home residents with advanced dementia experienced one or more neuropsychiatric symptoms during the six month period prior to enrollment in the

CareAD study. The most prevalent symptoms were agitation/aggression (50%), depression (46%), withdrawal/lethargy (43%), refusal/resistance (38%), and psychosis (27%), and aberrant motor (21%). The prevalence for most symptoms appears to be greater in our sample than in the 105 Cache County Utah residents with severe dementia reported by Lyketsos et al.⁷ In the Cache County Study, the most prevalent neuropsychiatric symptoms were: apathy (32%), agitation/aggression (29%), irritability (23%), depression (19%), aberrant motor behavior (19%), delusions (19%), and hallucinations (15%).

There are four possible reasons for the differences between the two studies. First, the participants with dementia in the current study all met criteria for hospice care near the end of life, while those in the Cache County sample were judged to have severe dementia based on their performance on the Clinical Dementia Rating Scale (CDR)³¹ and were likely to have less advanced dementia as a group. A second difference is that all CareAD subjects resided in a nursing home, while a portion of those in the Cache County sample lived at home. Third, the time periods differed between the two studies: up to six months in CareAD compared to one month in the Cache County study. Finally, the Cache County sample used the Neuropsychiatric Inventory (NPI)³² to identify symptoms, while this study relied on retrospective chart review, though both methods are based upon caregiver observations. Despite these differences, both studies indicated that the most prevalent neuropsychiatric symptoms in advanced dementia were agitation/aggression, withdrawal/lethargy (including apathy), and depression.

The LCA suggests a 3 group classification of neuropsychiatric symptom patterns in advanced dementia. The three classes differ in the frequency, but not the type of symptoms. The largest classes consisted of residents who exhibited low frequencies of neuropsychiatric symptoms (Class 1), and residents who exhibited withdrawal and lethargy (Class 3), while the smallest class (Class 2) consisted of individuals who exhibited agitation/aggression, psychosis, depression, and refusal/resistance. Residents with mood disturbance were not classified into a separate group; rather depression was present across all groups. Examination of the less well-fitting LCA 4- and 5-class solutions revealed that neither produces a clear depression or mood disorder class. Although previous studies have suggested a lower prevalence of symptoms of depression in severe dementia^{33–35}, our data suggest that the lack of a latent mood disorder class results from the association of depression with a wide range of neuropsychiatric symptoms, not from low prevalence. Anxiety was low in frequency across all groups, but it is possible that anxiety was expressed behaviorally (e.g., agitation, calling out) and without a recognizable affective component and thus documented only as disordered behavior such as agitation.

The agitated/psychotic class is consistent with previous reports of high associations between agitation and psychosis^{34,35} in individuals with dementia. The withdrawn/lethargic group shares similarities with apathy symptom clusters in advanced dementia that may reflect frontal or more widespread cortical dysfunction.^{10,36,37} The latent classes identified in this sample of individuals with advanced dementia overlap with classes identified in the two previous LCA studies. A low-frequency symptom class and an aggressive or agitated psychotic class were consistent across all three studies. The affective class identified by Lyketsos et al.¹⁸ and Moran et al.¹⁹ was replaced by a withdrawn and lethargic class in this sample. Symptoms of depression were common in the agitated/psychotic class (70%), and the withdrawn/lethargic class (44%), and similar in frequency to the affective disturbance classes identified by Lyketsos et al. (depression = 49%) and Moran et al. (affective disturbance = 45%). Whether this is due to a difference in how the depressive symptoms were ascertained, differences in populations sampled, or differences in how depression is expressed in different stages of dementia cannot be ascertained from these data.

Limitations

There are several limitations of the findings. First, neuropsychiatric symptoms and diagnostic type of dementia were gathered by retrospective medical chart review rather than use of standardized, validated instruments, and therefore may have been biased in the direction of recording only symptoms severe enough to warrant treatment. In addition, criteria for diagnosing depression and anxiety in late-stage dementia have yet to be validated. The finding in this study that the behaviors seen in depressed elderly individuals with no dementia and depressed individuals with mild and moderate stage dementia are also seen in persons with advanced dementia supports the use of these behaviors as markers for depression, though this deserves further study.

These data were collected in three facilities in urban and rural Maryland and may not be representative of facilities in other states or countries. Based on the retrospective nature of the data, it is not possible to determine whether the neuropsychiatric symptoms were due to the dementia, co-morbid medical illness, the environment, or medications. The phenomena of withdrawal/lethargy or apathy has been noted previously in nursing home residents with advanced dementia¹⁰, however we cannot rule out contributions from acute illness³⁸ or medications, since the study participants had multiple comorbidities and were taking multiple medications. Finally, these findings represent only a six month period, and we do not know how stable the latent classes remain over time.

CONCLUSION

By the late stages of dementia, it is likely that almost all areas of the brain are severely dysfunctional and classification by standard diagnostic criteria may hold less meaning than the classification by patterns of symptoms. The findings of the LCA that there are two non-normative syndromes or classes of neuropsychiatric symptoms in advanced dementia near the end of life, one characterized primarily by agitation and psychosis and the other by withdrawal and lethargy, requires validation. If valid neuropsychiatric syndromes can be identified, syndrome-specific intervention and drug studies may be warranted.³⁹ Because neuropsychiatric symptoms are associated with distress and impaired quality of life⁴⁰, such studies have the possibility of moving us closer to the overall goal of providing the highest quality care for individuals suffering from dementia.

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Table 1
Number and Percentage of Neuropsychiatric Symptoms in Advanced Dementia

Symptoms	Medical Record Descriptors	Dementia Types					
		All Types n=123		Alzheimer's n=71		Vascular n=13	
		n	%	n	%	n	%
Agitation/Aggression	agitation, aggression, combative, hitting, grabbing	62	50.4	36	50.7	7	53.8
Depression	depression, mood disorder, suicidal ideation, mood change, depression with psychosis	56	45.5	30	42.3	6	46.2
Withdrawal/Lethargy	withdrawal, lethargy, decreased socialization, fatigue, social isolation, apathy, social deficit, isolating self in room, sedation	53	43.1	34	47.9	3	23.1
Refusal/Resistance	refusal, resistance	47	38.2	29	40.8	4	30.8
Psychosis/Delusions	psychosis, delusions, delusional disorder, psychosis NOS, schizophrenia, catatonia	33	26.8	20	28.2	2	15.4
Aberrant motor	wandering, behavioral disturbance, nose picking, crawling, restlessness, smearing stools, picking	26	21.1	17	23.9	4	30.8
Sleep disorder	insomnia, sleep apnea, sleep wake cycle disturbance, drowsiness, awake most of night	17	13.8	8	11.3	2	15.4
Calling out	calling out, moaning in sleep	11	8.9	5	7.0	1	7.7
Anxiety	anxiety	10	8.1	8	11.3	0	0

Table 2
Model Fit Indices of the Latent Class Analysis of Neuropsychiatric Symptoms

Model	LogLi	NoPar	AIC	BIC	LRT	p	Entropy
2-class	-564.947	19	1167.894	1161.249	53.027	0.3761	0.672
3-class	-546.965	29	1151.930	1141.788	35.232	0.005	0.790
4-class	-541.127	39	1160.254	1146.614	11.439	0.511	0.826
5-class	-532.838	49	1163.675	1146.538	13.839	0.066	0.862

Note. LogLi= Loglikelihood; NoPar = the number of free parameters in the estimated model; AIC = Akaike information criterion; BIC = Sample-size adjusted Bayesian information criterion, LRT = Lo-Mendell-Rubin's adjusted likelihood ratio test.

Table 3

Probabilities of Neuropsychiatric Symptoms within Latent Classes

Symptoms	Class 1 (n=44) Low Symptoms	Class 2 (n=29) Agitated/Psychotic	Class 3 (n=50) Withdrawn/Lethargic
Agitation/aggression	0.178	0.913	0.499
Depression	0.284	0.698	0.436
Withdrawal/lethargy	0.000	0.454	0.726
Refusal/resistance	0.085	0.657	0.435
Psychosis/delusions	0.170	0.849	0.000
Aberrant Motor	0.000	0.209	0.364
Sleep disorder	0.027	0.295	0.127
Calling out	0.081	0.254	0.000
Anxiety	0.053	0.256	0.000

Table 4

Number and Percentage of Dementia Diagnostic Subtypes within Latent Classes

Dementia		Class 1 (n=44) Low Symptoms	Class 2 (n=29) Agitated/Psychotic	Class 3 (n=50) Withdrawn/Lethargic
Subtypes	n	n / %	n / %	n / %
Alzheimers	71	25/56.8	17/58.6	29/58.0
NOS	17	8/18.2	3/10.3	6/12.0
Mixed	15	5/11.4	4/13.8	6/12.0
Vascular	13	6/13.6	2/6.9	5/10.0
Lewy Body	3	0/0	1/3.4	2/4.0
Other	3	0/0	1/3.4	2/4.0
FTD	2	0/0	1/3.4	1/2.0
ALC	1	0/0	0/0	1/2.0
HIV	1	0/0	0/0	1/2.0
Parkinson's	1	0/0	1/3.4	0/0

Note. NOS = not otherwise specified; FTD = frontotemporal; ALC = Alcohol-related. Four individuals received more than one diagnosis of dementia in addition to those in the mixed category.