Causes of Aggressive Behavior in Patients With Dementia

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Objective: To examine factors predicting development of aggression.

Method: Community-dwelling patients over 60 years of age in a Veterans Affairs Medical Center who had a documented *ICD-9-CM* code for dementia within 12 months of screening and no other dementia codes recorded for 2 preceding years but no aggressive behavior during the 12 months preceding study initiation were assessed every 4 months for 24 months for aggression, depression, pain, patient/ caregiver relationship quality (mutuality), involvement in pleasant events, and caregiver burden. The study was conducted from September 5, 2003, to June 10, 2005.

Results: Of 215 patients, 89 (41%) developed aggression. In individual models, high baseline mutuality decreased risk of aggression; high burden and pain increased risk. Increases in depression and pain and declines in total mutuality also increased risk. In a full model and step-wise model, high levels of baseline caregiver burden, worst pain, and decline in mutuality over time increased risk of aggression.

Conclusions: Many dementia patients become aggressive. Higher levels of worst pain, caregiver burden, and declining mutuality over time increase risk of aggression.

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ost people with dementia manifest noncognitive L clinical symptoms,¹ which may include aggression. The incidence of aggression is unknown, however, partly because of failure to differentiate between aggression and agitation in much of the literature. The concept of agitation lacks consensual definition and often includes disparate behaviors (eg, wandering, hyperactivity, and negativity) that likely have different etiologies, treatment and prognosis.² Aggression is defined as verbal or physical action intended to harm. Treatment of aggression is problematic because of the limited efficacy and significant risks of morbidity and mortality associated with psychotropic medications,³⁻⁵ frequently the first line of treatment. Identifying precipitants of aggression should facilitate development of preventive strategies, potentially increasing use of nonpharmacologic therapies. No prior studies have examined potentially mutable precipitants of aggression.

The objective of this study was to conduct a longitudinal examination of nonaggressive patients newly diagnosed with dementia and identify factors predicting development of aggression. Guided by a combination of Algase and colleagues'6 needs-driven model and Ryden and colleagues'7 model of aggression, we posited that aggression is determined by multiple factors; and many causes are mutable. We focused on psychosocial mutable precipitants, ie, factors potentially treatable using effective interventions. Internal factors include depression, psychosis, pain, and dementia severity. External factors include social stimulation, caregiver burden, and quality of caregiver-patient relationship (mutuality). We hypothesized that a combination of these factors would predict onset of aggression. The literature lacks studies that prospectively and longitudinally link mutable precipitants with severe behavioral disturbances such as aggression. The prospective design of this study allows for stronger causal arguments than cross-sectional studies, which predominate this literature

METHOD

Recruitment of Participants

Newly diagnosed, nonaggressive dementia patients were identified through Veterans Administration Outpatient Data Files, flyers, radio and print advertisements, and the Michael E. DeBakey Veterans Affairs (VA) Medical Center primary care and geriatrics clinics. To be eligible, participants had to have been diagnosed with dementia during 2001 to 2004. A letter was sent to eligible subjects indicating that research staff would contact them unless they called to decline.

Inclusion/Exclusion Criteria

Inclusion criteria were age over 60 years and new diagnosis of dementia, defined as receiving an initial outpatient *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* code for dementia (290.XX, 291.2,292.82, 294.1,294.8, or 331.0) within 12 months before screening, with no other dementia codes recorded for 2 preceding years. Exclusion criteria were (1) aggressive behavior in the past year, (2) current residence in a nursing home, or (3) having a caregiver less than 8 hours per week. Dementia diagnoses were confirmed through medical records and caregiver report. Potential participants subsequently underwent telephone screening to verify eligibility criteria. Aggressive patients were excluded using 3 probes from the Ryden Aggression Scale⁸ regarding (1) unprovoked, deliberately unfriendly, or violent behavior, including hitting, pushing, and/or throwing things, cursing a person, calling people names, and using hostile and/or accusatory language; (2) physical aggression, such as hitting, pushing, or throwing things that caused physical injury to the patient, caregiver, or others; or (3) verbal aggression, such as making verbal threats to hurt people, cursing people, or accusing people of doing things, in a hostile manner. Once participants were enrolled, the full Ryden Aggression Scale was used to confirm that aggressive behaviors had not been present during the previous year. Further details regarding the recruitment/screening process have previously been described.⁹

This research was approved by the Houston VA Research and Development Committee and the Baylor College of Medicine Institutional Review Board. Patients and caregivers provided written informed consent. The study was conducted from September 5, 2003, to June 10, 2005.

Instruments for Assessing Aggression (dependent variable)

Aggression was evaluated using the Cohen-Mansfield Agitation Inventory (CMAI),¹⁰ which relies on a 7-point Likert scale for frequency and a 5-point Likert scale for disruptiveness. It yielded both categorical and continuous scores; total scores summed all 29 frequency and distress ratings (range, 58 to 377). Aggression was considered present if a participant scored over 0 on both frequency and disruptiveness on the total aggression subscale, comprising any of 13 questions referring to spitting, cursing/ verbal aggression, hitting, kicking, grabbing, pushing, throwing, biting, scratching, hurting self/others, tearing things/destroying property, making inappropriate verbal sexual advances, or making inappropriate physical sexual advances.

Instruments for Assessing Independent Variables

Intrinsic determinants. Depression. The Hamilton Depression Rating Scale (HDRS-17) was used to assess depression.¹¹ It is both valid and reliable for older adults with depression, including those with dementia.¹² With the adapted HDRS,¹² the clinical rater combines information from observations with an interview of both patient and caregiver. Possible scores range from 0 to 68 (10 to 13, mild; 14 to 17, mild-to-moderate; and > 17, moderate-to-severe depression).¹¹

<u>Psychosis.</u> The Neuropsychiatric Inventory (NPI) delusions and hallucinations subdomains¹³ were used to assess psychosis. For both these subscales, a positive response by the dementia patient's primary caregiver to any of 10 screening questions leads to a score consisting of frequency×severity (4- and 3-point scales, respectively). Possible scores range from 1 to 12 for each domain.

<u>Pain.</u> Pain was measured using the Philadelphia Geriatric Center Pain Intensity Scale¹⁴; we used 2 scale items assessing worst and least pain over the preceding 4 weeks. If pain is endorsed, patients evaluate how much it has interfered with daily activities, on a 5-point scale (1 = not at all, 2 = a little, 3 = some, 4 = quite a bit, 5 = a great deal). This scale has been shown to have adequate internal consistency and test-retest reliability in persons with dementia.¹⁴

Extrinsic determinants. <u>Caregiver burden</u>. The Burden Interview¹⁵ measures perceived impact of caregiving on caregiver's financial/physical status, physical/emotional health, and social activities. This scale, specifically developed for caregivers of dementia patients, has well-established validity and reliability. It uses a 22-question Likert scale questionnaire with 5 options, from 0 to 4. Range of scores is 0 to 88 (0 to 20, little or no burden; 21 to 40, mild-to-moderate burden; 41 to 60, moderate-to-severe burden; and 61 to 80, severe burden).

<u>Quality of patient-caregiver relationship.</u> The Mutuality Scale¹⁶ measures the positive quality of the relationship between a family caregiver and care receiver and has been used with caregivers of patients with Alzheimer's disease.¹⁷ The scale is composed of 15 items describing the frequency (not at all, 0; a little, 1; some, 2; quite a bit, 3; a great deal, 4) of communication, positive engaging interactions, attachment, and emotional support. We used the Mutuality Scale total score, representing the mean of all items.

<u>Social stimulation</u>. The Pleasant Events and Activities Schedule Alzheimer's Disease (short version)¹⁸ was used to measure frequency and perceived enjoyment of participation in 2 domains of activity: passive-active and social-nonsocial. It was developed and validated with community-dwelling individuals with dementia and has well-established internal consistency.¹⁸ We used the Pleasant Events and Activities Enjoyment score, a continuous measure of how much 20 different activities are enjoyed (yes = 1, no = 0). Possible range is 0 to 20.

Instruments for Assessing Cognitive Impairment

The Dementia Rating Scale (DemRS2)¹⁹ is a standardized measure of general cognitive ability designed to screen for cortical impairment, particularly of the degenerative type, such as Alzheimer's disease. It has been shown to have adequate internal consistency, test-retest reliability, and convergent and predictive validity.¹⁹

Schedule of Assessments

Participants and caregivers were assessed monthly for 24 months, during home visits at baseline and 4-month intervals (eg, months 5, 9, 13, 17, 21, and 25 and by telephone in other months). All instruments were administered at each visit except the DemRS2, administered at baseline only.

Analyses

Incidence of aggression. The yearly incidence rate of new aggression was estimated by dividing number of participants becoming aggressive by total number of years "at risk." The at-risk period for each participant was the length of time from baseline assessment until the end of study follow-up or aggression onset. Total time at risk for the sample was the sum of individual participants' periods at risk.

Descriptive analyses. We tested for simple differences between our aggressive and nonaggressive samples on our covariates (demographic characteristics and dementia severity) and baseline psychosocial measures. We used χ^2 tests for our categorical measures (sex, race-ethnicity) and *t* tests for our continuous measures.

Primary analyses. We used Cox proportional hazards models to estimate associations between predictive variables and onset of aggression. Predictor variables of interest included depression, psychosis, pain, caregiver burden, social stimulation, and quality of caregiver-patient relationship. All models were adjusted for patients' age, sex, race, and baseline measure of dementia severity.

We modeled relationships between change in predictor variables over time and likelihood of aggression onset; for example, does change in depression predict the likelihood of becoming aggressive? We estimated the change over time between each participant's baseline observation and last observation before censoring by calculating the slope of change across all available study observations for each individual. Since multiple observations are necessary to calculate change, only participants with 2 or more observations were included in our analysis. All change estimates were scaled to represent change over 12 months.

We ran 3 sets of Cox proportional hazards models. First, we estimated relationships between baseline values for predictive variables and onset of aggression. Next, we estimated a combined model for each predictor variable, including both baseline values and those representing change over time. Finally, we developed a full model by combining all our predictive variables into a single multivariate model. We also ran a stepwise selection procedure using our full set of predictive measures, adjusting first for our covariates.

RESULTS

Description of Cohort

Recruitment yielded 615 potentially eligible participants for prescreening. Most (91% or 562) were successfully contacted. Of those, 71% (400) consented to participate, 5% refused screening, and 22% opted out or declined; 2% of caregivers refused to consent.

All 400 patients who successfully prescreened and verbally consented were screened by phone. Most (81%, or 325) were not aggressive, according to caregivers. Nineteen percent (75 of 400) acknowledged aggressive behavior, as follows: 31% verbal, 12% physical, 32% both verbal and physical, and 25% unspecified. These patients were excluded. For the 325 patients screening negative for aggression, we attempted to schedule and complete baseline home visits. Some participants were unreachable (n = 13, or 4%). Thirty-three percent (n = 107) were excluded because their baseline home-visit assessment indicated aggression or other exclusion criteria. A total of 215 (66%) newly diagnosed patients (and caregiver dyads) were successfully enrolled. Mean age was 76 years (SD±6.2). Most (95.4%) were men because of the predominance of men in the

VA system. Approximately 76% were white, 20% were black, and 4% were of other race. Twenty-nine patients were taking antipsychotic medications at baseline.

Incidence

Eighty-nine (41%) patients developed aggression over 24 months. Fifty-three (60%) had aggression causing moderate or severe distress, and 54 (61%) had aggression occurring at moderate or severe frequency. In addition, 41 patients (46%) had physical, 72 (81%) had verbal, and 13 (15%) manifested sexual aggression. We calculated the unadjusted incidence of aggression by dividing total number of aggressive patients (n = 89) by total number of years at risk for our entire cohort (number of years = 237.6). The unadjusted incidence of aggression was 0.37 cases per year at risk.

Comparison of Aggressive Versus Nonaggressive Patients

Significant baseline differences between those who developed aggression and those who did not were observed in dementia severity, depression, mutuality, burden, delusions, and hallucinations (Table 1). The distribution of dementia severity into severe, moderate, and mild was 56 (45%), 21 (17%), and 47 (38%) in the nonaggressive group compared with 56 (66%), 14 (17%), and 14 (17%) in the aggressive group, respectively. The mean dementia severity score at baseline was significantly lower among patients who developed aggression than among those who did not (P=.004), indicating that they were more impaired than those that did not develop aggression; the mutuality score was also significantly lower for patients who developed aggression (P=.002). Mean scores for depression (P=.02), hallucinations (P=.004), delusions (P=.007), and caregiver burden (P=.0001) were higher among patients who developed aggression than among those who did not. Only 20 patients had hallucinations or delusions; as expected, there was an association between hallucinations/delusions and antipsychotic use (P < .001). Potentially, this could have diminished the psychotic risk for aggression. However, given the low frequency of psychosis, further analyses were not done. No significant differences in gender, age, race, pain, or enjoyment of pleasant events were observed. Use of antipsychotics at baseline (n = 29) was not associated with development of aggression (P=.31). The reasons for antipsychotic use in these patients were previously published; but, in summary, depression (n = 17; 59%), nighttime disturbance (n = 15; 52%), and hallucinations (n = 13; 45%) were the most often documented neuropsychiatric symptoms.²⁰ Only 7 additional patients were given antipsychotics during follow-up. Given this low number, an additional analysis was not warranted.

Individual Models

We conducted 8 Cox proportional hazards analyses examining the association between onset of aggression and each potential determinant at baseline and over time, adjusting for age, sex, race, and dementia severity. Aside from onset of aggression, other reasons for censoring nonaggressive patients included withdrawal from the study (n = 43;

Table 1. A Comparison of Potential Determinants of
Aggression at Baseline Between Patients Who Developed
Aggression and Patients Who Did Not (N=215)

	Aggressive	Nonaggressive	P		
Variable	(n = 89)	(n=126)	Value		
Male, n (%)	86 (96.63)	119 (94.44)	.45		
Age, mean (SD), y	76.88 (6.16)	75.81(6.19)	.13		
Race, n (%)					
White	65 (73.03)	99 (78.57)	.14		
Black	18 (20.22)	25 (19.84)			
Other	6 (6.74)	2 (1.59)			
DemRS2 total score, mean (SD)	3.02 (2.38)	4.12 (2.79)	.004		
HDRS total score, mean (SD)	7.36 (4.61)	6.16 (5.28)	.02		
Mutuality Scale, total score,	2.89 (0.65)	3.14 (0.74)	.002		
mean (SD)					
Philadelphia Geriatric Center					
Pain Intensity Scale score,					
mean (SD)					
Pain now	0.72 (1.25)	0.81 (1.13)	.27		
Pain worst	2.00 (1.78)	1.91 (1.53)	.94		
PES total score, mean (SD)	16.75 (3.36)	17.13 (3.10)	.50		
Burden Interview score,	24.16 (14.31)	14.73 (12.21)	.0001		
mean (SD)					
Neuropsychiatric Inventory					
score, mean (SD)					
Delusion	0.69 (1.94)	0.28 (1.27)	.007		
Hallucinations	0.62 (1.76)	0.23 (1.07)	.004		
Abbreviations: DemRS2 = Dementia Rating Scale, HDRS = Hamilton					

Depression Rating Scale, PES = Pleasant Events and Activities Enjoyment.

20%), nursing-home placement (n = 17, 8%), and death (n = 28, 13%).

As noted, our models specifically included measures of change for our predictive factors. Twenty-five patients were excluded because of onset of aggression before their first follow-up visit, resulting in data from only 1 visit. An additional 16 patients were excluded because of attrition (n = 1) or incomplete baseline data (n = 15). In addition, 3 subjects had extreme outlying change scores for hallucinations, producing an anomalous association between change in hallucinations and onset of aggression. Omission of these individuals from analyses did not affect findings for other measures. Our final-analysis sample included 171 patients with complete baseline and change-score data. No significant differences were observed between the 44 excluded patients and the 171 patients in age, gender, race, depression, mutuality, pleasant events, pain now, pain worst, caregiver burden, and delusions. However, higher baseline scores for hallucinations were observed among excluded patients.

Results for our individual models are shown in Table 2. For baseline measures, higher total Mutuality Scale scores (P=.006) at baseline were associated with decreased risk of onset of aggression, while higher levels of caregiver burden (P=.0001) and worst pain (P=.03) were associated with increased risk. For our change measures, increases over time in depression (P=.04) and current pain (P=.05) and declines in total mutuality (P=.0001) were also associated with increased risk of aggression.

Full and Stepwise Models

In our full model (Table 3), higher levels of baseline caregiver burden (P=.002), worst pain (P=.01), and decline Table 2. Results From 6 Individual Cox Proportional Hazards Models Examining the Effect of Depression, Mutuality, Pain, Pleasant Events, and Caregiver Burden at Baseline on the Risk of Aggression, With Adjustments for Age, Sex, Race, and Dementia Severity (n = 171)

	Hazard		
Measure	Ratio	95% CI	P Value
HDRS			
Baseline	1.05	0.99-1.11	.07
Change over time	1.06	1.00-1.12	.04
Philadelphia Geriatric Center			
Pain Intensity Scale score			
Pain now			
Baseline	1.10	0.86 - 1.40	.45
Change over time	1.26	1.00 - 1.57	.05
Pain worst			
Baseline	1.24	1.03-1.49	.03
Change over time	0.96	0.83-1.11	.56
Neuropsychiatric Inventory score			
Delusion			
Baseline	1.07	0.88-1.31	.47
Change over time	1.16	0.99-1.35	.06
Hallucinations			
Baseline	1.03	0.83-1.28	.79
Change over time	0.93	0.73-1.19	.57
Mutuality Scale, total score			
Baseline	0.63	0.45 - 0.87	.006
Change over time	0.46	0.33-0.66	.0001
PES score			
Baseline	0.94	0.87-1.02	.15
Change over time	0.94	0.87 - 1.00	.06
Burden Interview score			
Baseline	1.05	1.03 - 1.07	.0001
Change over time	1.03	0.99-1.05	.08
Abbreviations: HDRS = Hamilton D	epression Ra	ting Scale,	

PES = Pleasant Events and Activities Enjoyment.

in mutuality over time (P = .006) were independently associated with increased risk of aggression, controlling for other psychosocial measures and covariates. These findings were confirmed in our stepwise selection model, which indicated that higher levels of baseline worst pain (adjusted hazard ratio [HR] = 1.28; 95% CI, 1.901–1.537), caregiver burden (adjusted HR = 1.04; 95% CI, 1.022–1.062), and decline in mutuality over time (adjusted HR = 0.55; 95% CI, 0.383–0.781) were associated with increased risk. No other predictive measures were independently associated with risk of aggression, either in the full or stepwise model.

DISCUSSION

We found potentially mutable factors internal and external to the patient associated with development of aggression. This has important preventive and treatment implications for the almost 40% of dementia patients that become aggressive each year. Our longitudinal design and sample of newly diagnosed, previously nonaggressive dementia patients strengthen prior findings in the literature. The focus on the more specific behavior of aggression, rather than agitation, is more likely to align causes and potential interventions.

Incidence

A few community-based studies have determined the prevalence of *agitation-aggression*, using different

Table 3. Results From a Cox Proportional Hazards Model Examining the Effect of Change in Depression, Mutuality, Pain, Pleasant Events, and Caregiver Burden on the Risk of Onset of Aggression, With Adjustments for Age, Sex, Race, and Dementia Severity (N = 171)

	Hazard		
Measure	Ratio	95% CI	P Value
HDRS			
Baseline	0.99	0.93-1.06	.79
Change over time	1.04	0.98-1.10	.23
Philadelphia Geriatric Center			
Pain Intensity Scale score			
Pain now			
Baseline	0.83	0.60-1.13	.24
Change over time	1.03	0.81-1.31	.81
Pain worst			
Baseline	1.41	1.08 - 1.84	.01
Change over time	1.03	0.87 - 1.22	.77
Neuropsychiatric Inventory score			
Delusion			
Baseline	1.09	0.77 - 1.54	.63
Change over time	1.14	0.98 - 1.32	.08
Hallucinations			
Baseline	0.95	0.70 - 1.29	.73
Change over time	0.83	0.62 - 1.11	.21
Mutuality Scale, total score			
Baseline	0.87	0.55 - 1.37	.55
Change over time	0.50	0.31-0.82	.006
PES score			
Baseline	1.02	0.93-1.13	.67
Change over time	1.02	0.95-1.10	.61
Burden Interview score			
Baseline	1.04	1.01 - 1.06	.002
Change over time	1.00	0.97 - 1.04	.88
Abbreviations: HDRS = Hamilton De Pleasant Events and Activities Enio	epression Ra	ting Scale, PES	S=

instruments, with prevalence ranging from 24% in the preceding month²¹ to 30%–50% for aggression in different population samples^{1,22–25} to $35\%^{25}$ to $64\%^{26}$ of community-dwelling persons with aggression.

Four longitudinal studies of aggression found rates ranging from 10% (6-month incidence) to 31% (1-year incidence).²⁷⁻³⁰ However, the comparability of these estimates is limited by differences in the definition of aggression, specifically, the degree to which aggression and agitation were differentiated.

The Cache County study found a 16% 18-month incidence of agitation/aggression,³⁰ and a study of a representative sample of patients with Alzheimer's disease living in homes and long-term care facilities found a 22% incidence.²⁹ Our 37% 1-year incidence is slightly higher than that found in previous studies. However, unlike previous studies, our study population was predominately white male veterans. Prior studies have found higher rates of aggression among whites; however, no studies have identified differences in rates of aggression by gender. We are not aware of any studies that have examined rates of aggression among veterans.

Factors Contributing to Development of Aggression

Up to 90% of persons with dementia manifest noncognitive clinical symptoms, such as delusions, hallucinations, depression, irritability, agitation, and aggression,¹ associated with caregiver distress and burden, excess disability, rapid cognitive decline, and early institutionalization.³¹ Much of the literature does not distinguish between aggression and agitation.

Associations between aggression and determinants internal and external to the patient have been demonstrated, including depression,³² psychosis,³² pain,³³ caregiver burden,³⁴ quality of caregiver-patient relationship,³⁴ and social stimulation.³⁵ Only 1 of the 4 longitudinal studies referenced above examined precipitants of aggression, finding that low cognitive status and poor functional ability were predictors.²⁸

Pain. Our results suggest that painful experiences, particularly extreme worst painful experiences, are important in development of aggression. Correlational studies of pain and agitation have consistently linked the two; but correlational studies of pain and aggression have been more equivocal.³⁶ This is, to our knowledge, the first longitudinal study to examine the relationship between pain and aggression. Moreover, this study focused on self-reported, rather than caregiver-reported, pain. It is interesting that pain ratings obtained by asking participants to rate current pain were significant in the individual model yet became insignificant in predicting aggression in the full model when ratings of the worst pain experience over the past week were also included. Our findings imply, not surprisingly, an overlap in these pain questions. But, further, they imply that ratings of worst pain were most informative with regard to predicting onset of aggression. Thus, how one asks about pain in important. Untreated pain in persons with dementia is associated with significant negative outcomes, including increased health care use,37 inactivity and isolation.³⁸ Our findings underscore the importance of routine pain assessment and appropriate pain treatment in this population.

Depression. In our unadjusted analyses, increases in depressive symptoms predicted onset of aggression. Past studies also highlight this relationship. Three cross-sectional studies in nursing homes³⁹⁻⁴¹ and 1 in outpatients³² show relationships between aggression and depression in persons with dementia. Similarly, 2 longitudinal studies found that sad or depressed affect predicted aggression in communitydwelling dementia patients⁴² and adult day-care attendees.³³ These findings replicate a consistent and growing body of literature implicating a relationship between depression and aggression and support practice-guideline recommendations for pharmacologic and nonpharmacologic interventions for depression in persons with dementia.43 However, our multivariate analyses suggest that the relationship of depression with onset of aggression may be mediated by the other factors in our model (pain, mutuality, and caregiver burden), and that the link between depression and aggression onset may be partially indirect.

Psychosis. We found that increases in delusions over time, consistently predicted aggression, but hallucinations did not; prior studies have, mostly, reached similar conclusions. For example, although 3 cross-sectional studies of outpatients

found delusions and hallucinations more common in aggressive patients,³² 1 such study found an association for delusions but not hallucinations.²³ A cross-sectional study of patients attending a dementia clinic showed that overt aggression and agitation are the most frequent behavioral concomitants of delusions in Alzheimer's disease⁴⁴; and Leonard et al40 found that physical aggression was associated with delusions and hallucinations in the nursing home. In 2 longitudinal observational studies, delusions but not hallucinations were associated with aggression.⁴⁵ Thus, delusions appear to be more consistently associated with aggression than do hallucinations. However, the inconsistent relationship with hallucinations might be attributable to the low prevalence of hallucinations in this population. In our sample, those with hallucinations were more likely to develop aggression than those without hallucinations before the first follow-up and, thus, to be excluded from analysis. However, only 20 patients in our cohort had hallucinations or delusions. Because hallucinations/delusions were significantly associated with antipsychotic use, it is possible that this could have diminished the psychotic risk of aggression.

An important implication of identifying this association is that one should treat psychosis to attempt to prevent aggression. However, several recent controlled trials and meta-analyses failed to show a separation of the placebo response from the antipsychotic response for behavioral problems of dementia.⁴ Although antipsychotics are still the mainstay of treatment,⁴³ considering their morbidity and mortality,^{3–5} the provider should frankly discuss risks and benefits of their use with the patient and family. The field clearly needs new treatment options.

Burden and mutuality. In the full model, we found that patients whose caregivers reported more burden at baseline and less mutuality (or lower quality of relationship) over time became aggressive sooner. Mutuality and caregiver burden are modifiable and amenable to intervention, which should focus on helping the dyad maintain or foster quality relationships that include support, activity, and psychoeducation.

Caregiver-oriented interventions have received recent support. Two recent trials found improved neuropsychiatric symptoms in patients and caregivers⁴⁶ and caregiver quality of life.⁴⁷ These findings are consistent with earlier literature reviews⁴⁸ and a meta-analysis⁴⁹ supporting targeting caregivers to improve quality of life for patient-caregiver dyads. Most indicated that earlier, more frequent intervention was best and that interventions targeting multiple sources of caregiver stress and both caregiver and patient were most effective in reducing negative outcomes (eg, depression, caregiver burden, institutionalization) and increasing positive outcomes (eg, subjective well-being, caregiver satisfaction).

This study lends additional support to the concept of intervening in the caregiver-patient relationship to improve caregiver satisfaction and reduce potential for patient aggression.

Looking Forward: An Integrated Model of Aggression Prediction

The importance of both intrinsic and extrinsic psychosocial variables is clearly suggested by our findings, as shown by the significant predictive performances of 5 of 8 individual models in Table 2. However, the specific mechanisms by which such factors affect aggression are less clear, as indicated by the varying results, depending upon analytic context: mean scores of some, but not all, baseline variables were significantly different between aggressive and nonaggressive individuals, whereas other variables became significant in the multiple logistic regression model including all potential predictors of aggression (Table 3). Such varying results strongly suggest complex interrelationships among psychosocial variables. The strong interrelationship between depression and pain is well documented,⁵⁰ but there is scant literature on interrelationships between some of our other predictor variables and certainly no work to date looking at the interrelationship of the wide variety of predictor variables included in our work.

Prevention of aggression is the clinical goal. Development of a multifactorial model of aggression prediction should ultimately result in the ability to develop risk assessments for aggression; to be clinically useful, these should focus on clinical targets amenable to change. Our study represents an integral step in this process being, to our knowledge, the first to combine a wide variety of psychosocial variables in a longitudinal design to highlight the complexity of relationships between intrinsic and extrinsic variables and predictive relationships between them and aggression. It is clear from our results, particularly the stepwise analyses, that pain, mutuality, and caregiver burden play a seminal role in aggression development. It is reasonable to hypothesize that psychosis, depression, and level of cognitive impairment are also associated with aggression but perhaps in an indirect relationship.

Limitations

The strength of this study is its longitudinal design, standardized repeated measures, and inception sample of patients with new (rather than recent-onset) diagnosis of dementia and no aggression. Such a sample and design strengthen predictive/causal findings. However, the study has limitations. We did not differentiate types of dementia because we largely relied on diagnoses by primary care physicians, who do not usually specify type; and we had attrition at all stages of the project. We also admit that differences between groups in depression and mutuality scores were small and of unknown clinical significance. Furthermore, it is possible that excluded aggressive patients may have had more severe dementia than patients who were included in our analyses. Our study sample was limited, largely, to male veterans because of their predominance in the military. However, compared with many studies of dementia, our sample, and older veterans in general, are more representative of older adults in the population in regards to race/ethnicity, socioeconomic groupings, and education.⁵¹

CONCLUSIONS

Behavioral therapy to address behavioral disturbance has best evidence to date. In addition, targeted psychoeducation designed to improve communication around caregiving issues may be helpful^{52,53} and improve outcomes. Studies aimed at preventing onset of aggression are needed that specifically address factors that might contribute to aggression. Given that antipsychotics remain the predominant treatment for aggression,⁵⁴ and that they can have serious side effects, the need for such studies is urgent.

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