


Sex Differences in the Neuropsychiatric Symptoms of Patients With Alzheimer's Disease

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Abstract

The aim of this study was to describe sex differences in neuropsychiatric symptoms (NPSs) in patients with Alzheimer's disease (AD). Baseline scores on the Cohen-Mansfield Agitation Inventory, Neurobehavioral Rating Scale–Agitation subscale, and the Neuropsychiatric Inventory from patients with AD enrolled in a multicenter trial of citalopram for the treatment of agitation were analyzed. We found not only that patients with AD having agitation were likely to exhibit many other NPSs but also that the women in this study were more likely to exhibit a broader range of NPS than were the men. These results suggest greater heterogeneity in the clinical presentation of women compared to men, and thus in the potential targets for treatment in these patients. Further characterization of sex differences in NPS can inform future efforts aimed at establishing subtypes of patients for whom various treatment approaches will be most appropriate.

Keywords

Alzheimer disease, agitation, behavioral disturbance, gender difference, neuropsychiatric

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, affecting an estimated 5.7 million persons in the United States in 2018.¹ Although cognitive decline is a cardinal feature of AD, the concurrent development of neuropsychiatric symptoms (NPSs) during the course of the illness is more often the rule than the exception.² Because these symptoms incur additional functional impairment and caregiver burden, successful amelioration of them is an essential component of treatment.

It has long been established that the prevalence of AD is higher in women than in men,³ and more recently, sex differences in the clinical and pathological manifestations of the disease have been described. These differences suggest potential mechanisms underlying disease pathogenesis and are valuable in informing potential targets for treatment. In contrast to the myriad studies aimed at elucidating the neuropathological underpinnings of AD, sex differences in AD-associated NPS have received scant research attention.

Although several studies have described sex differences in NPS in patients with all-cause dementia,⁴⁻¹⁰ these studies do not describe NPS in AD specifically or have been confounded by sex differences in comorbid conditions.¹¹ Given that different forms of dementia can be associated with different NPS,

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focusing on a specific etiology of dementia may be useful in better characterizing sex differences in specific symptoms. In patients with vascular dementia, for example, women are more likely than men to have delusions, hallucinations, and depression; men are more likely than women to exhibit apathy.¹² Men with Parkinson disease are more likely to be verbally and physically aggressive, preoccupied with bodily functions, and predisposed to wandering, while women with this illness have more depressive symptoms.¹³ In a residential care facility, demented women were more likely to be depressed; men were more aggressive and more likely to engage in inappropriate behaviors.⁶ In older persons with major depression, men exhibit more agitation and women more appetite disturbances.¹⁴

In outpatients with AD,¹⁵ caregivers rated women as more reclusive and more likely to hoard, refuse help, and exhibit inappropriate laughter or crying compared to men. Men, in contrast, were rated as exhibiting behaviors more indicative of psychomotor changes (apathy, pacing) and vegetative changes (excessive eating and sleeping). In another study of outpatients with AD, women were more likely than men to exhibit multiple psychiatric problems; 47.6% of women had 2 or more psychiatric symptoms, compared to 39.8% of men.¹⁶ Statistical comparisons of the prevalence for each psychiatric symptom were not performed. The authors also found that in women, agitation was associated with all psychiatric symptoms except for apathy and delusions, whereas in men, agitation was associated with only paranoia.

We sought to examine sex differences in NPS in AD in a secondary analysis of data obtained through a clinical trial for the treatment of agitation in patients with AD. Because agitation is among the most distressing symptom for caregivers of patients with dementia,¹⁷ identifying effective treatment options will have significant impact to public health. Prior studies have found that in patients with dementia, men with agitation are more likely to be treated with antipsychotics than are women with agitation.¹⁸ Whether this sex difference in agitation treatment is due to sex differences in co-occurring neuropsychiatric symptoms (NPSs) in patients with agitation is not known. In this study, we sought to explore sex differences in NPSs that co-occur with agitation. We compared men and women on specific symptoms of agitation as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) and the Neurobehavioral Rating Scale (NBRs)¹⁹ and on broader NPSs as reflected by Neuropsychiatric Inventory (NPI) ratings. Because our sample was restricted to patients exhibiting agitation severe enough to warrant treatment, we suspected that the women in our study were more severely behaviorally disturbed than the typical woman with AD. For this reason, we hypothesized that the number of NPS would be higher in women than in men. Based on findings from prior studies, we also hypothesized that men would exhibit a greater number of physical symptoms of agitation—particularly verbal and physical aggression—whereas women would be more likely than men to exhibit affective symptoms.

Methods

This cross-sectional cohort analysis examines baseline data from the Citalopram for Agitation in Alzheimer's Disease (CitAD) clinical trial. The CitAD study methods have been published elsewhere.²⁰ In brief, CitAD is a randomized, double-masked, placebo-controlled multicenter clinical trial, with 2 parallel treatment groups assigned in a 1:1 ratio with randomization stratified by treatment center. Patients were recruited from 8 clinical centers, a chair's office, and a coordinating center located in university settings in the United States and Canada. Individuals having probable AD with clinically significant agitation were recruited for the study. Exclusion criteria were meeting criteria for major depressive episode by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; having another brain disease that may cause dementia; or current treatment with antipsychotics, anticonvulsants (other than dilantin), other antidepressants (other than trazodone, ≤ 50 mg/d at bedtime), benzodiazepines (other than lorazepam), or psychostimulants. The final sample of 186 patients was randomized to receive citalopram (target dose of 30 mg/d) or matching placebo. Data from the baseline visit, prior to randomization, were analyzed for the current study.

Agitation was assessed with the short (14-item) form of the CMAI, and the Agitation subscale of the NBRs (NBRs-A).²¹ The CMAI asks caregivers to rate symptoms of agitation on a 7-point scale ranging from "never" to "several times an hour".⁵ Specific behaviors on the CMAI were reduced to 4 factors for analysis: physically nonaggressive (specific symptoms of which were general restlessness, repetitious mannerisms, pacing trying to get to a different place, handling things inappropriately, hiding, and inappropriate dressing or undressing), physically aggressive (ie, hitting, pushing, scratching, grabbing things, grabbing people, kicking, biting), verbally nonaggressive (ie, negativism, doesn't like anything, constant requests for attention, verbal bossiness, complaining or whining, relevant interruptions, irrelevant interruptions, and repeating sentences), and verbally aggressive (ie, screaming, cursing, temper outbursts, and making strange noises).

The NBRs-A quantifies clinician ratings of 3 aspects of agitation (disinhibition, motor manifestations of agitation, and hostility) in a 7-point scale ranging from 0 ("not evident") to 6 ("extremely severe"). Neuropsychiatric symptoms were measured using the NPI.^{22,23} The 12 domains included in the NPI are as follows: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime disturbances, and appetite/eating change. The frequency and severity of each symptom are rated by a caregiver on a 4-point and 3-point Likert scale, respectively. A composite score can be calculated for each symptom by multiplying the frequency and severity scores, and scores for the total scale range from 0 (no symptoms) to 144.

Demographic data were collected and verified by a caregiver or other collateral informant. Caregiver distress was measured using the NPI Caregiver Distress scale,²⁴ an adjunct scale

Table 1. Demographic and Population Descriptors of Participants by Sex.

Characteristic ^a	Mean (SD)/No. (%)		P Value ^a	Characteristic	Mean (SD)/No. (%)		P Value ^a
	Women n = 85	Men n = 101			Women n = 85	Men n = 101	
Age, mean, years	79.8 (7.5)	77.2 (9.0)	.04	Duration of dementia, mean, years	4.6 (3.7)	5.2 (4.2)	.28
Race, no.			.04	Marital status, no.			<.01
White	46 (54%)	74 (73%)		Married	29 (34%)	83 (82%)	
African American	20 (24%)	11 (11%)		Widowed	39 (46%)	11 (11%)	
Hispanic/Latino	13 (15%)	11 (11%)		Separated or divorced	9 (11%)	3 (3%)	
Other	6 (7%)	5 (5%)		Never married	8 (9%)	4 (4%)	
Highest education, no.			.12	Sex of caregiver, No.			<.01
No high school diploma	27 (32%)	25 (25%)		Male	40 (47%)	13 (13%)	
High school diploma	25 (29%)	18 (18%)		Female	45 (53%)	88 (87%)	
Some college/associate's degree	10 (12%)	19 (19%)		Relationship of caregiver to participant, no.			<.01
Bachelor's degree	15 (18%)	22 (22%)		Spouse or significant other	25 (29%)	71 (70%)	
Professional/graduate degree	8 (9%)	17 (17%)		Child or grandchild ^b	47 (55%)	19 (19%)	
Residence, no.			.02	Other family member ^b	5 (6%)	4 (4%)	
Own home	56 (66%)	84 (83%)		Paid caregiver ^c	6 (7%)	4 (4%)	
Caregiver's home	13 (15%)	12 (12%)		Friend	2 (2%)	3 (3%)	
Assisted living	4 (5%)	0 (0%)		NPI caregiver distress, mean	15.8 (8.1)	17.6 (8.8)	.15
Nursing facility	7 (8%)	2 (2%)		MMSE	14.5 (6.3)	16.8 (6.8)	.02
Other	5 (6%)	3 (3%)		ADCS-ADL Scale	39.8 (19.2)	45.4 (17.5)	.04

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; MMSE, Mini-Mental State Examination.

^aT test for continuous variables, χ^2 or Fisher exact test for categorical variables.

^bCharacteristics are at the time of enrollment.

^cIncludes in-laws.

^dIncludes in-home care and clinicians in care facilities.

to the NPI for assessing the impact of NPS in patients with AD on caregiver distress. The Mini-Mental State Examination (MMSE)²⁵ was used as a measure of global cognition. The Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)²⁶ scale, with higher scores indicating greater functional independence, was used to assess everyday functioning.

Statistical analyses were completed using SAS version 9.2 and R version 2.13.1. Demographic, socioeconomic, and clinical variables that have been shown to be associated with sex in previous literature were included as potential confounders and were compared for women versus men using *t* tests for continuous variables and χ^2 or Fisher exact test for categorical variables.

The distribution of the total number of 14 CMAI agitation symptoms that were present and the total number of the NPI NPS symptoms that were present were compared by sex using a Kruskal-Wallis nonparametric test. The outcomes of the 4 CMAI factors (physically nonaggressive behaviors, physically aggressive behaviors, verbally nonaggressive behaviors, and verbally aggressive behaviors), NBRs-A subscale scores, and NPI symptoms scores were highly skewed, and linear regression methods requiring normality were not appropriate. Therefore, the CMAI factors were categorized as dichotomous variables at the median. The NBRs-A responses of 0 and 1 (“not evident” and “very mild”) were categorized as “absent”, and all other responses were categorized as “present.” Each NPS from the NPI was categorized as a dichotomous

presence/absence variable. Logistic regression was used to model associations between sex and the 4 CMAI factors, the individual NBRs-A subscales, or individual NPI symptoms, and the test for significance was a Wald χ^2 . The unadjusted models were univariate models of sex versus the CMAI, NBRs-A, or NPI outcome.

Adjusted models were multivariate, including control for all potential confounders from Table 1 that were significant at the 20% level²⁷ (all variables from Table 1 except duration of dementia). Because of small cell sizes, categories had to be collapsed for the following variables in order to fit the models: race as white versus others, marital status as married versus others, education as high school or less versus greater than high school, residence as own home versus others, and caregiver as spouse/significant other versus others. Relationships between the confounders were assessed using Spearman correlation coefficients (for 2 continuous/ordinal variables), χ^2 or Fisher exact test (for 2 unordered categorical variables), or analysis of variance (for a continuous and categorical variable). Inflation of the variance due to multicollinearity of the covariates was assessed by calculating the variance inflation factor (VIF) using linear regression. None of the calculated VIF reached the level generally considered as concerning²⁸; however, sensitivity analyses with fewer covariates were considered and are discussed below.

Adjusted models were not calculated for the NPI “elation/euphoria” due to a small number of events. For the NPI outcomes, a second model was constructed using linear regression

Table 2. Cohen-Mansfield Agitation Inventory (CMAI) and Neurobehavioral Rating Scale–Agitation (NBRSA) Unadjusted and Adjusted Odds Ratios (ORs) by Sex.

Scale	Prevalence at Enrollment			Unadjusted		Adjusted ^a	
	All, N = 186	Women, n = 85	Men, n = 101	Women vs Men		Women vs Men	
				OR (95% CI)	P Value ^a	OR (95% CI)	P Value ^a
Cohen-Mansfield Agitation Inventory, ^b n (%)							
Physically nonaggressive behaviors	86 (46%)	44 (52%)	42 (42%)	1.5 (0.8-2.7)	.17	0.8 (0.3-2.0)	.65
Physically aggressive behaviors	64 (34%)	34 (40%)	30 (30%)	1.6 (0.9-2.9)	.14	1.7 (0.8-4.0)	.19
Verbally nonaggressive behaviors	68 (37%)	38 (45%)	30 (30%)	1.9 (1.0-3.5)	.04	2.0 (0.9-4.5)	.11
Verbally aggressive behaviors	84 (45%)	39 (46%)	45 (45%)	1.1 (0.6-1.9)	.86	1.0 (0.5-2.3)	.95
NBRSA, ^c n (%)							
Disinhibition	68 (37%)	33 (39%)	35 (35%)	1.2 (0.7-2.2)	.56	1.3 (0.6-3.1)	.53
Agitation–motor manifestations	130 (70%)	65 (76%)	65 (64%)	1.8 (0.9-3.4)	.07	1.5 (0.6-3.8)	.39
Hostility	126 (68%)	61 (72%)	65 (64%)	1.4 (0.8-2.6)	.28	1.2 (0.5-2.8)	.67

Abbreviation: CI, confidence interval.

^a Test for significance is a Wald χ^2 . Unadjusted models are univariate models of sex versus the outcome. Adjusted models are multivariate including control for all covariates included in Table 1, except duration of dementia. The OR is for women versus men.

^b Outcome defined as a symptom score higher than the median and modeled by logistic regression.

^c Outcome defined as rating of “moderate,” “moderately severe,” “severe,” or “extremely severe.”

of the log of NPS frequency \times severity values including only those participants experiencing the symptom (frequency \times severity score > 0), and comparisons by sex were made using linear regression adjusting for all covariates. These data are not shown because the results were not meaningfully different.

Sensitivity analyses were performed for both the CMAI and NPI outcomes by including fewer covariates to reduce potential variance inflation. In the first sensitivity analysis, confounders were excluded if they were statistically associated with another confounder in the model: ADL (Spearman $\rho = 0.70$, 95% confidence interval [CI]: 0.62-0.77) and years of education (Spearman $\rho = 0.31$, 95% CI: 0.17-0.43) were associated with MMSE, and both ADL and education were excluded; residing in the participant's own home and being married (Fisher exact $P < .001$) were associated, and residence was excluded. Caregiver relationship and being married (Fisher exact $P < .001$) were associated, and caregiver relationship was excluded. In the second sensitivity analysis, variables for inclusion were selected by forcing sex to be included as a covariate and then using stepwise regression with liberal entry and exit criteria ($P = 0.15$) to select the remaining covariates. Results for both sensitivity analyses were similar to the results with the fully adjusted model described above and are shown in Supplemental Tables 1, 2, and 3.

Results

Participant Characteristics

As shown in Table 1, at enrollment, men and women were well matched for level of education and level of distress reported by their caregivers. Otherwise, women were slightly older than men, less likely to be Caucasian, and less likely to live in their own homes compared to men. Women were also less likely than men to be married; not only were they much more likely

to be widowed, but they were also more likely to be separated or divorced or never married. Accordingly, over half of the women were cared for by a child or grandchild, whereas the majority of men were cared for by a spouse or significant other. Also of note is that men had higher MMSE scores (for men: mean = 16.8, standard deviation [SD] = 6.8, for women: mean = 14.5, SD = 6.3) and were more functionally independent than were women as measured by the ADCS-ADL scale.

Symptoms of Agitation on the CMAI

The distribution of the total number of CMAI symptoms that were present was higher in women (median of 7 symptoms [Q1, Q3: 4, 8]) compared to men (median of 5 [Q1, Q3: 4, 7]), Kruskal-Wallis $P = .01$.

Regarding the nature of agitation as assessed by the CMAI (Table 2), women were more likely than men to engage in verbally nonaggressive behaviors (1.9 [1.0, 3.5]) in the unadjusted model. Although this difference was no longer statistically significant after adjusting for all covariates, the effect size of the sex difference actually increased. Men and women were equally likely to exhibit physical manifestations of agitation and to engage in verbally aggressive behaviors. With regard to specific behaviors, verbal aggression, repetitive speech, and complaining or refusal to follow directions were the most common symptoms in both sexes. On single-variable analysis of the CMAI (see Supplemental Table 2), the unadjusted model revealed that women were more likely than men to engage in pacing or aimless wandering (1.9, 95% CI: 1.1-3.4; $P = .03$), complaining or refusal to follow directions (2.5, 95% CI: 1.1-5.7; $P = .03$), and hiding or hoarding things (2.0, 95% CI: 1.1-3.6; $P = .02$). Adjusting for all covariates, these differences no longer reached statistical significance. Examination of the

Table 3. Neuropsychiatric Inventory (NPI) Unadjusted and Adjusted Odds Ratios (ORs) by Sex.

NPI ^a Domain, no. (%)	Prevalence at Enrollment			Unadjusted		Adjusted ^b	
	All, n = 186	Women, n = 85	Men, n = 101	Women vs Men		Women vs Men	
				OR (95% CI)	P Value ^c	OR (95% CI)	P Value ^c
Delusions	78 (42%)	45 (53%)	33 (33%)	2.3 (1.3-4.2)	.01	2.2 (0.9-5.1)	.07
Hallucinations	39 (21%)	19 (22%)	20 (20%)	1.2 (0.6-2.4)	.67	1.2 (0.4-3.3)	.75
Agitation/aggression ^c	186 (100%)	85 (100%)	101 (100%)	—	—	—	—
Depression/dysphoria	95 (51%)	41 (48%)	54 (53%)	0.8 (0.5-1.4)	.48	0.7 (0.3-1.7)	.44
Anxiety	121 (65%)	62 (73%)	59 (58%)	1.9 (1.0-3.6)	.04	2.3 (1.0-5.3)	.05
Elation/euphoria ^d	13 (7%)	7 (8%)	6 (6%)	1.4 (0.5-4.4)	.54	—	—
Apathy/indifference	114 (61%)	45 (53%)	69 (68%)	0.5 (0.3-0.9)	.03	0.7 (0.3-1.7)	.48
Disinhibition	95 (51%)	41 (48%)	54 (53%)	0.8 (0.5-1.4)	.48	1.1 (0.5-2.8)	.77
Irritability/lability	157 (84%)	74 (87%)	83 (82%)	1.5 (0.6-3.3)	.36	4.4 (1.4-14.1)	.01
Motor disturbance	96 (52%)	46 (54%)	50 (50%)	1.2 (0.7-2.1)	.53	1.2 (0.5-2.9)	.64
Nighttime behaviors	85 (46%)	40 (47%)	45 (45%)	1.1 (0.6-2.0)	.73	0.7 (0.3-1.7)	.48
Appetite/eating	86 (46%)	36 (42%)	50 (50%)	0.7 (0.4-1.3)	.33	0.6 (0.2-1.4)	.23

Abbreviation: CI, confidence interval; NPI, Neuropsychiatric Inventory.

^aPresence/absence of symptom modeled by logistic regression, test for significance is a Wald χ^2 .

^bAdjusted models are multivariate, including control for all covariates included in Table 1.

^cAll participants had NPI agitation at baseline due to eligibility criteria.

^dAdjusted model not calculated due to small number of events.

change in effect sizes in the adjusted model reveals small decreases compared to the unadjusted model.

Symptoms of Agitation on the NBRSA

Clinicians rated the presence of symptoms of agitation similarly in men and women (Table 2). The percentage of women exhibiting motor manifestations of agitation was slightly higher than the percentage of men rated as manifesting this symptom (1.8, 0.9-3.4]; $P = .07$) in the unadjusted model. In the fully adjusted model, this trend was no longer apparent, although the effect size for the difference increased.

Neuropsychiatric symptoms on the NPI

Examination of broader NPS as assessed by the NPI indicated that agitation—present in 100% of the sample by design—was almost always accompanied by other NPS. With the exception of elation and hallucinations, each NPS was present in at least 40% of the sample. The distribution of the total number of NPI NPS symptoms that were present did not differ by sex (median [Q1, Q3] in women: 6 [5, 8] and in men: 6 [5, 7]), Kruskal-Wallis; $P = .31$.

On single-variable unadjusted analysis of the NPI, women were more likely than men to exhibit delusions (2.3, 95% CI: 1.3-4.2; $P = .01$) and anxiety (1.9, 95% CI: 1.0-3.6; $P = .04$), whereas men were more likely to exhibit apathy (0.5, 95% CI: 0.3-0.9; $P = .03$). After adjusting for covariates, the additional NPS of irritability/lability was more likely in women than men (4.4, 95% CI: 1.4-14.1; $P = .01$), and no single NPS was higher in men than in women (Table 3). As with the CMAI, effect sizes for the differences between men and women did not

change substantially after adjustment, suggesting that a lack of power to detect the differences after adjusting for the covariates was an issue.

Among participants experiencing the NPI symptom of interest, the results comparing frequency by severity scores were similar to the dichotomous presence/absence results (data not shown) except that the log of NPI sleep frequency \times severity scores were lower for women than for men (-0.27 , 95% CI: -0.49 to -0.05 ; $P = .02$), even though similar numbers of men and women reported any sleeping difficulties.

Discussion

In this study, we compared NPS in men and women with AD who were part of a clinical trial for the treatment of agitation. Our first hypothesis was that the number of NPS would be greater in women than in men. Regarding symptoms of agitation specifically, women had a broader range of symptoms on the CMAI than did men. Unadjusted models revealed women to have more verbally nonaggressive behaviors and more pacing/aimless wandering compared to men. The significance of these differences did not, however, survive adjustment for all of the covariates. Regarding the presence of broader NPS (NPI total scores), men and women did not differ. Comparison of specific symptoms indicated that women were more likely than men to pace/wander, complain, and hide/hoard things as measured by the CMAI and to experience anxiety, irritability, and possibly delusions as measured by the NPI. Men, in contrast, were more likely to exhibit apathy as measured by the NPI. A trend toward greater likelihood of motor manifestations of agitation in women compared to men on the NBRSA was also found.

Our second hypothesis was that men would be more likely to exhibit verbal and physical aggression, whereas women would be more likely to have affective symptoms. Contrary to our prediction, we found that if anything, women were slightly more likely than men to exhibit several of these symptoms. Although no particular symptom appeared to dominate women's manifestation of agitation, there was a trend for women to be more likely than men to engage in physically aggressive behaviors.

Regarding our hypothesis that compared to men, women would have more affective symptoms, women did tend to have more anxiety than men, and the effect size for this difference actually increased after adjusting for the covariates. In contrast, we found no sex difference in depression, which was surprising given that depression is more common in women than in men. However, we note that the sex difference in prevalence of depression diminishes after menopause,²⁹ suggesting that our finding might have been expected. It is also of note that agitation might be considered a symptom of depression; the primary finding from the CitAD study was that citalopram improved agitation in these patients.³⁰ Thus, the women in our study might have had more depression than the men, but because it was manifested as agitation, the sex difference was evident only by comparison of total CMAI score rather than by classic symptoms of depression assessed by the NPI. This notion is also supported by findings from at least one study that found agitation in women was related to multiple symptoms, including depression, insomnia, paranoia, hallucinations, and emotional lability, whereas agitation in men was associated with only paranoia.¹⁶ In another study, dementia severity predicted both agitation and depression, but severity of depression also predicted increased aggressive behavior.³¹ These studies underscore the relatedness among NPS and suggest sex differences in these associations.

It is noteworthy that not only did the patients in this study exhibit agitation but they also exhibited a range of other NPS; indeed, in only 2 patients was agitation the sole NPS. Although the 3 most common NPS were irritability/lability, anxiety, and apathy/indifference, only 2 of the NPS (elation and hallucinations) were present in fewer than 40% of the sample. This finding suggests that in patients with agitation, pervasive NPS are likely.

We reported our findings for both unadjusted models and models adjusted for demographic characteristics. Whether one considers the unadjusted or adjusted models as primary warrants mention. For this study, we were interested in describing potential sex differences in symptoms of agitation and broader NPS. Some of the covariates we entered in the models are difficult to tease apart from the quality of being an elderly man or woman. Marital status and relationship of caregiver to participant, for example, are confounded with sex, given that women are more likely than men to outlive their spouses. Although adjustment for these types of variables allows one to speculate about potential biological underpinnings for our observed differences, the goal of this study was simply descriptive. Although most of the effect sizes in the unadjusted models did not change substantially after adjustment for covariates, we

included both models to facilitate comparison between our findings and those of future studies.

The primary limitation of our study is that only patients with AD enrolled in a treatment study for agitation were included. Because participants enrolled in the treatment study were selected on the basis of exhibiting moderate and frequent agitation, sex differences in the manifestation of agitation were most likely suppressed. Our findings may not therefore be generalizable to the entire AD population. Comparison of our sample to a sample of patients with AD having comparable MMSE scores, but who were not recruited specifically due to seeking treatment for agitation, yields some insight into the generalizability of our sample. Specifically, patients with AD enrolled from consecutive evaluations in an outpatient clinic had a slightly higher prevalence of sleep disturbance and depression compared to the patients in our study, but otherwise had much lower rates of other NPS as queried by the NPI.³² These findings suggest that agitation in particular, rather than simply dementia severity, portends global behavioral disturbance. These findings further support the notion that agitation may be more aptly considered a manifestation of a number of other conditions rather than a singular behavioral disturbance.

It is possible that our current sample may include a more severely behaviorally disturbed population of women with AD compared to a more typical sample of men with AD. That the sample comprised a greater number of men than women, which is opposite from most studies in patients with AD, would support this idea. However, in a sample of never-treated patients with AD,³³ men and women did not differ with regard to a "psychomotor" syndrome, which subsumes agitation. Because the current study was not designed to examine sex differences in NPS, there was limited power to fully explore factors related to our findings. Dementia severity in particular might play a role in sex differences in NPS. Patients in the current study had MMSE scores ranging from 5 to 28. Studies have documented that verbal agitation, disinhibition, irritability, delusions, and depression are more prevalent in moderate cognitive decline, whereas in patients with severe cognitive decline, apathy, hallucinations, anxiety, and physical aggression are more prevalent.⁷ We note that MMSE scores were higher in men than in women in the current study; it is possible that the magnitude and/or characteristics of sex differences in NPS varies over the course of cognitive decline.

Conclusions

Agitation encompasses a spectrum of behavioral disturbances related to dementia, which may each respond with different efficacies to different classes of antipsychotics and antidepressants. In patients with AD who were enrolled in a treatment study for agitation, we found that women had a greater number of NPS compared to men. Given sex differences in response to, and pharmacodynamics of, psychoactive medications,³⁴ future studies aimed at further characterizing the nature of sex differences in NPS among patients with AD will be valuable in suggesting future targets for treatment. Because not every

patient responds to treatment for agitation, efforts to establish phenotypes that predict treatment response have become a focus of recent work. Findings from the current study may inform such efforts to develop subtypes of patients most likely to respond to various types of intervention.


Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Porsteinsson is a board member on Data Safety and Monitoring Boards for Quintiles, Functional Neuromodulation, and New York State Psychiatric Institute; participated on a speaker's bureau for Forest; and developed educational presentations for CME, Inc. Dr Pollock reports being a board member on Data Safety and Monitoring Boards for Lundbeck Canada; is a paid consultant for Wyeth; and has received travel and accommodation expenses from Lundbeck International Neuroscience Foundation. Dr Porsteinsson is a paid consultant for Elan, Janssen Alzheimer Initiative, and Pfizer. Dr Ismail reports being paid for lectures by Calgary Foothills Primary Care Network, Calgary West Central Primary Care Network, Canadian Conference on Dementia, Alberta College of Family Physicians, and University of British Columbia and is a paid consultant for Astra Zeneca, Janssen, Lundbeck, Otsuka, Pfizer, and Sunovion. Dr Rabins reports being paid for legal testimony from Janssen. Dr Devanand is employed by Roper St. Francis Healthcare, Medical University of South Carolina, Ralph H. Johnson VA Medical Center, and NeuroQuest and is founder of BioPharma Connex. Dr Rosenberg is a paid consultant for Janssen and Pfizer and has developed educational presentations for Eli Lilly. Dr Schneider reports being a board member on Data Safety and Monitoring Boards for Eli Lilly and Janssen and receiving royalties from Oxford University Press. Dr Munro is a paid consultant for Forest Laboratories, Eli Lilly, Astra Zeneca, Johnson and Johnson, Bristol Myers Squibb and Otsuka, and Abbott and Abbvie.

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Supplemental Material

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