

# Anxiety in Alzheimer's Disease: Prevalence and Comorbidity

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**Background.** Anxiety may be associated with psychiatric morbidity, disability, increased health care utilization, and mortality in Alzheimer's disease (AD) patients as it is in the general adult population. However, the phenomenology of anxiety symptoms in AD and its relationship to dementia progression, comorbid depression, and the presence of other problematic behaviors have not yet been examined.

**Method.** Data on anxiety symptoms and their coexistence with other factors were obtained in 523 community-dwelling AD patients through interviews with their caregivers and direct physical examination. The prevalence of anxiety symptoms and their association to patient depression, other behavioral problems, gender, and age was investigated.

**Results.** Anxiety symptoms were common, occurring in 70% of subjects. Anxiety symptoms were significantly correlated with ADL impairment and other behavioral disturbances, including wandering, sexual misconduct, hallucinations, verbal threats, and physical abuse. Comorbidity of anxiety–depression was also prevalent: 54% of the sample had both anxiety and depression symptoms. ADL impairment and problem behaviors were significantly associated with comorbidity; however, the latter association was explained entirely by the presence of anxiety.

**Conclusion.** Anxiety symptoms were common and significantly related to ADL and additional neuropsychiatric problems in this sample. These results indicate the need for additional research into the phenomenology of anxiety and comorbid anxiety–depression in AD and for the development and investigation of effective assessment and treatment of anxiety in AD clinical practice.

THE neuropsychiatric and behavioral concomitants of Alzheimer's disease (AD) have been the subject of increasing research interest in the past decade. However, symptoms of anxiety have received relatively little attention. Within the general population, anxiety disorders are known to be associated with psychosocial morbidity, disability, and mortality (1). Among elderly adults, anxiety disorders are also associated with increased and possibly excessive medical care utilization (2).

Although rarely studied in their own right, when examined in studies of general behavioral symptoms in AD, anxiety symptoms consistently emerge as common. For example, four studies of AD outpatients using three different, well established scales found that 25%–60% of subjects had anxiety symptoms, including anxiety, irritability, agitation, day/night disturbance, and motor restlessness (3–5). The rate of anxiety symptoms among both hospitalized and community-dwelling AD patients is higher than that in healthy elderly peers (4,6,7).

The association of anxiety to depression in AD patients, however, is unknown. In nondemented elderly adults, there is significant comorbidity between anxiety and depression whether one refers to symptoms or diagnostic entities (8). In a recent review, Schneider (9) noted that between one- and two-thirds of elderly individuals with clinically significant (DSM-III-R) anxiety or depression meet American Psychiatric Association criteria for both disorders. Given that the prevalence of depression in AD is quite high, with rates reported as high as 87% (10) and averaging 30% (11), it is conceivable that comorbid anxiety and depression may affect a large percentage of patients with AD.

Little is also known about the relationship of anxiety to other neuropsychiatric and problematic behaviors in AD, such as argu-

ing, combativeness, destruction of property, and wandering. One might hypothesize that anxiety would be positively related to such disturbances but again, whether or not this is true is unknown.

In summary, the literature on anxiety in AD, to date, indicates that anxiety may well exist in a subset of patients. However, the nature of anxiety symptoms in AD patients, and the relationship of anxiety symptoms to comorbid depression, the presence of other problematic behaviors, and dementia progression have not yet been examined in AD samples. This article presents data on anxiety symptoms and their comorbidity in an incidence sample of 523 community-dwelling AD patients. The prevalence of specific anxiety symptoms and their association to depression, other behavioral problems, patient gender, and age was investigated.

## METHOD

### Procedures

Subjects were part of an ongoing, community-based Alzheimer's Disease Patient Registry (ADPR) established in 1987 cooperatively between the University of Washington and Group Health Cooperative of Puget Sound (GHC), a major health maintenance organization in Seattle with about 23,000 persons over age 60. The ADPR attempts to identify all GHC patients with dementia symptoms as they first come to medical attention. Such identification is provided by a surveillance network consisting of primary care physicians, logs of CT scans, neurology and other clinic visits, as well as computerized treatment record files and hospital discharge files, medical chart reviews, and nurse interviews with identified cases. Additional de-

tails regarding the base population and procedure can be found elsewhere (12). Once identified, patients are followed over time to monitor changes in their functional and cognitive status.

Each patient identified by the ADPR received a comprehensive, multidisciplinary diagnostic evaluation. The evaluation included (a) a 1–2-hour intake interview conducted by an experienced research nurse with the patient and an informant (e.g., concerned caregiver, family member, or friend); (b) complete physical and neurological exam conducted by an internist or a neurologist (both specializing in geriatrics), and (c) a standardized neuropsychological screening battery that was administered by a trained psychometrician and interpreted by a geriatric psychologist. Final diagnoses were based on the results of all evaluations presented and discussed at consensus meetings attended by a psychiatrist, psychologist, internal medicine physician, neurologist, epidemiologist, and research staff.

### Subjects

For this study, only those ADPR subjects who met the National Institute of Neurologic and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA; (13)] criteria for "probable" ( $n = 439$ ) or "possible" ( $n = 84$ ) AD were included. The mean age at intake was 79.3 years ( $SD = 6.9$ ), with a range of 48 to 99 years; 64% of subjects were female, 89% were Caucasian, and 49% were married. Thirty-seven percent had post-high school education. Forty-five percent lived with their spouse, 38% lived alone, and 17% lived with others. Seventy-four percent of subjects had been experiencing cognitive problems for less than 3 years.

### Measures

**Cognitive/functional ability.**—Cognitive ability was assessed using the Mini-Mental State Exam [MMSE; (14)] and the Mattis Dementia Rating Scale [MDRS; (15–16)]. The mean MMSE score for the present sample was 20.4 ( $SD = 4.9$ ); the mean MDRS score was 113.1 ( $SD = 16.4$ ).

Functional ability was evaluated using the Blessed Dementia Rating Scale [BDRS; (17)]. For this report, a composite variable was created from five BDRS items that pertain to activities of daily living (ADLs): eating, dressing, toileting, performing household tasks, and coping with small sums of money. The composite reflected the number of ADL behaviors in which the patient required assistance and ranged from 0 to 5. Subjects displayed difficulty in an average of 1.3 ( $SD = 1.3$ ) ADL behaviors, with most (81%) evidencing difficulty in fewer than three areas.

**Behavioral symptoms.**—Behavioral symptoms, including anxiety, depression, and other problematic behaviors, were evaluated from a 21-item behavior checklist for which items were rated as present or absent by the physician conducting the physical examination, based upon observation of the patient and information provided by the informant (18,19).

The assignment of symptoms to anxiety or depression classification was based on the consensus of a team of psychologists (LT, RL, SM, LF) using DSM-IV criteria, and guided by theory (20). Symptoms reflective of an aroused or activated state of emotional distress were assigned to anxiety, and symptoms reflective of a deactivated state of emotional distress were assigned to depression. Assignment of symptoms as problem behaviors

was determined by exclusion from the former two categories and included behaviors that represent difficulties typically encountered in AD patients that are potentially problematic in patient care and management. All symptoms were selected from an established dementia checklist reported previously (18,19).

A composite anxiety score was created from four items on this checklist: anxious/fearful/apprehensive, agitated/restless, irritable/easy to anger, suspicious/paranoid. Each symptom was assigned a weight of 1, with the exception of the item *anxious*, which was weighted more heavily (weight = 2) because it assessed anxiety most directly. The average anxiety score was 1.9 ( $SD = 1.7$ ; range 0–5). Fifty-seven percent of subjects had an anxiety score of 2 or greater (Table 1). This group could be considered to have clinically significant anxiety symptomatology. The symptom *anxious* and at least one other symptom were endorsed for 168 (56%) of these subjects; 61 (20%) endorsed only *anxious*.

A depression score was created using the same strategy. Of the four items pertaining to depression, three items (socially withdrawn, appears inactive, tearful/cries) were assigned a weight of 1, and the fourth and most relevant (depressed) was assigned a weight of 2. The average depression score was 1.5 ( $SD = 1.4$ ; range 0–5). Forty-three percent of subjects had a depression score of 2 or greater (Table 1). The symptom *depressed* and at least one other symptom were endorsed for 47% of the subjects who had depression scores  $\geq 2$ ; 20% endorsed only *depressed*. Subjects who scored  $\geq 2$  on anxiety and  $\geq 2$  on depression may be considered to have clinically significant comorbid symptomatology.

A composite problem behavior score was created by summing five equally weighted items that were not representative of anxiety or depression: wandering, sexual misconduct/preoccupation, hallucinations, verbal threats/accusations, physical belligerence/abuse. Subjects displayed an average of 0.5 ( $SD = 0.8$ ; range 0–5) problem behaviors. The majority of subjects (87%) displayed fewer than two problem behaviors.

**Associated characteristics.**—The following variables were also included in the analyses because of their reported or potential relationship to anxiety and depression: age, gender, ethnicity, marital status, residence (residing in one's own home vs other type of residence), education, and duration of dementia symptoms.

### Statistical Analyses

Data were analyzed using SPSS and Stata. Four groups of subjects were analyzed: (a) the total sample ( $N = 523$ ), consisting of subjects with and without anxiety symptoms; (b) the sub-

Table 1. Weighted Anxiety and Depression Scores in AD Patients ( $N = 523$ )

Weighted Score	Anxiety		Depression	
	<i>n</i>	%	<i>n</i>	%
0	159	30	166	32
1	66	13	132	25
2	110	21	104	20
3	88	17	71	14
4	52	10	37	7
5	48	9	13	2

set of subjects ( $n = 457$ ), for whom anxiety scores were dichotomized 0 (no anxiety symptoms present,  $n = 159$ ) or  $\geq 2$  (anxiety or two other anxiety symptoms endorsed,  $n = 298$ ); (c) subjects with *any* comorbid symptoms ( $n = 280$ ). These subjects had at least *one* anxiety symptom *and* at least *one* depression symptom; (d) subjects who could be classified into one of four categories: no anxiety and no depression, anxiety ( $\geq 2$ ) without depression, depression ( $\geq 2$ ) without anxiety, and comorbid anxiety–depression ( $\geq 2$  on both,  $n = 343$ ).

Logistic regression analyses were conducted to identify variables associated with the presence of anxiety, using the dichotomized composite scores. Anxiety without depression, depression without anxiety, and comorbid anxiety–depression groups were simultaneously compared with the no anxiety or depression group using polytomous logistic regression. All variables with univariate  $p$  values  $<.20$  were candidates for the multivariate models, but only those with multivariate  $p$  values  $<.05$  were included. In the modeling process, plausible confounders and interactions were examined, but none was significant. Model fit, the scale of each variable, and the influence of outliers were also assessed. Because this is a cross-sectional study, prevalence odds ratios were calculated.

## RESULTS

### Anxiety

Symptoms of anxiety were common in this sample of AD subjects. Seventy percent had one or more symptom: 44% percent were anxious, fearful, or apprehensive; 36% irritable and easy to anger; 34% agitated and restless; and 33% suspicious and paranoid.

Anxiety was significantly related to behavior problems and ADL impairment. When subjects with anxiety scores of two or more ( $n = 298$ ) were compared to those without symptoms ( $n = 159$ ), the number of problem behaviors (wandering, sexual misconduct, hallucinations, verbal threats, physical abuse) was strongly associated with anxiety. The prevalence odds ratio (OR) was 4.2, which is to say that each additional problem behavior increased the odds of significant anxiety fourfold [95% confidence interval (CI) = 2.7, 6.6]. When the individual problem behaviors were examined, all five were univariately associated with anxiety. The odds ratios were 9.2 (3.9,21.6) for verbal threats, 5.0 (2.4,10.4) for hallucinations, and 3.7 (1.4,9.7) for wandering. All subjects exhibiting sexual misconduct or physical abuse were classified as anxious. Of all the factors considered, problem behaviors were the only factors to remain significant in multivariate

modeling of anxiety. Subjects requiring assistance with a greater number of ADL tasks were also more likely to be anxious than those requiring less assistance (OR = 1.4, 95% CI = 1.2,1.6): performing household tasks (OR = 1.6, 95% CI = 1.1,2.3), coping with money (OR = 2.6, 95% CI = 1.7,4.1) and dressing (OR = 2.3, 95% CI = 1.3,4.0) were each significantly associated to anxiety.

Anxiety was significantly related to level of cognitive impairment. Subjects with *more* severe cognitive impairment were more likely to be anxious than those with mild to moderate cognitive impairment, as measured by the MDRS (OR = 1.3 for a 20-point decrease in the MDRS, 95% CI = 1.0,1.7) and on the MMSE (OR = 1.2 for a 5-point decrease in the MMSE, 95% CI = 1.0,1.5).

Gender was not significantly related to overall level of anxiety, although there were gender differences in symptom presentation. Males were significantly more likely to be irritable/angry (OR = 1.9, 95% CI = 1.3,2.7) and agitated/restless (OR = 1.7, 95% CI = 1.2,2.5).

### Comorbidity

More than half of the sample (54%) had comorbid symptoms of anxiety and depression. The specific number of comorbid anxiety and depression symptoms in this sample is shown in Table 2. Among the subgroup of subjects with comorbid symptoms ( $n = 280$ ), 37% had at least two symptoms of anxiety and two symptoms of depression, 11% had at least three symptoms of each, and 2% had at least four symptoms of each.

To investigate this further, symptom-composite scores and four categories of comorbidity were developed (as already described). Groups defined by these four categories did not differ significantly on any of the demographic variables or on cognitive status (MMSE). The percentage of subjects in each category is shown in Table 3. The relative prominence of the comorbid category is revealed by examining values within the matrix. The category of comorbid anxiety–depression had the greatest number of subjects (45%), followed by the category of no anxiety/no depression (24%). The presence of either affective condition alone was the least common (13% and 18%). In other words, if subjects displayed significant affective symptoms, they were more likely to have comorbid symptoms than anxiety or depression alone. Similar comorbidity was observed when the specific symptoms of anxiety and depression were compared: 43% of the subjects were rated both anxious and depressed.

### Prediction of Comorbidity

Polytomous logistic regression was used to identify variables that were significantly associated with the different comorbid

Table 2. Number of Anxiety and Depression Symptoms in AD Patients ( $N = 523$ )

Number of Symptoms	Depression					<i>n</i>	%
	0	1	2	3	4		
Anxiety	0	82	45	26	5	159	(30%)
	1	32	49	32	12	127	(24%)
	2	32	42	29	13	117	(22%)
	3	12	26	15	16	72	(14%)
	4	8	14	13	7	48	(9%)
	<i>n</i>	166	176	115	53	13	
	%	(32%)	(34%)	(22%)	(10%)	(2%)	

Note: Values reflect the number of subjects with a particular number of anxiety and depression symptoms.

categories (Table 4). Anxiety without depression, depression without anxiety, and anxiety with depression groups were compared with the no anxiety–no depression group. Problem behaviors were strongly associated with anxiety in subjects both with and without accompanying depression. However, ADL impairment was significantly related to anxiety only among the subjects who were also depressed. Younger age was also associated with comorbidity in the multivariate model. This regression analysis was repeated on the alternative categorization (0 vs  $\geq 1$  behaviors) to assure that findings were not an artifact of categorization. Results were the same.

#### Probable and Possible AD

Because the sample included patients with both probable and possible AD, all analyses were repeated and restricted to only those 439 subjects with probable AD to determine whether the categorization of probable or possible AD influenced results. Findings were the same. The largest percentage of patients (54%) had comorbid symptomology; comorbidity was most associated with increased behavior and ADL problems; and anxiety was most significantly related to the higher disability associated with comorbidity.

#### DISCUSSION

This study investigated the prevalence and comorbidity of anxiety symptoms in a sample of 523 community-dwelling patients with AD. The phenomenology, prevalence, and association of anxiety to depression, other behavioral problems, level of cognitive and functional impairment, patient gender, and age were investigated.

Results indicate that anxiety symptoms were prevalent in this sample: 70% had one or more symptoms, with anxiety/fearfulness/apprehension being the most common (44%). These findings are consistent with earlier studies of general behavioral problems that reported comparable rates of anxiety-type symptoms in AD

samples (3–5). In this study, anxiety symptoms were significantly related to problems with ADLs and other behavioral disturbances, including wandering, sexual misconduct, hallucinations, verbal threats, and physical abuse. Indeed, there was a fourfold increased risk of anxiety with each additional behavioral problem.

Men were more likely to be angry and agitated; women were more likely to have symptoms of anxiety/fearfulness/apprehension. The finding of greater agitation in males is consistent with other studies of AD samples (4). Most studies of AD patients have found either greater anxiety among females as compared to males (21), or no gender differences (4,7,22).

Comorbid anxiety–depression was also common, with more than half the sample (54%) affected. This preponderance of comorbidity was true whether subjects had one, two, or more symptoms of anxiety or depression. Thus, if significant affective symptoms were present, they were more likely to present as a mixed-symptom picture.

ADL impairment and problem behaviors such as verbal threats, hallucinations, wandering, physical abuse, and sexual misconduct were significantly associated with comorbid anxiety–depression. However, the association to problem behaviors was explained entirely by the presence of anxiety, and the association with ADL impairment was explained by the presence of depression. Thus, it is possible that association of impairment to depression in previous studies may be attributable to anxiety. This possible confound needs to be investigated further.

Of all the factors considered in this study (including subject age, gender, cognitive level, etc.), ADL impairment and problem behaviors were the only consistent predictors of anxiety in both univariate and multivariate analyses. Parmelee and colleagues (23) also found reduced ADL functioning significantly related to anxiety in institutionalized older adults. To date, no other studies have investigated the role of anxiety or comorbidity with ADL impairment in AD.

The present study provides important data concerning the prevalence and comorbidity of anxiety and depression symptoms in AD. The goals of this research were to identify the prevalence and comorbidity of anxiety in a population of AD patients. There is a fundamental issue of how anxiety (and for that matter, depression and problem behaviors) should be defined or measured. For our purposes, we selected items that were consistent with well-established clinical criteria and theoretical concepts. Several methodological limitations in study design, however, constrain generalization of these results. First, as part of a larger epidemiological study on incidence rates in AD, physician ratings of anxiety and depression symptoms were em-

Table 3. Number of AD Patients in Affective Status Categories ( $N = 343$ )†

Anxiety (composite score)	Depression (composite score)	
	No Depression (0)	Depression (2+)
No anxiety (0)	82 (24%)	44 (13%)
Anxiety (2+)	63 (18%)	154 (45%)

†180 subjects with composite anxiety or depression scores equal to 1 were not included in this table.

Table 4. Polytomous Logistic Regression Modeling for Anxiety and Depression†

Predictor Variables	Symptom Group		
	Anxiety Only ( $n = 63$ ) OR (95% CI)	Depression Only ( $n = 44$ ) OR (95% CI)	Anxiety & Depression ( $n = 154$ ) OR (95% CI)
Number of problem behaviors	3.9 (2.0, 7.8)***	0.8 (0.3, 2.4)	3.7 (2.0, 7.2)***
Number of ADL impairments	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)	1.5 (1.1, 1.9)**
10-year decrease in age	1.3 (0.7, 2.2)	1.1 (0.6, 1.9)	1.8 (1.1, 2.7)*

†Odds ratios with confidence intervals that exclude one indicate factors that are significantly different compared with subjects with no anxiety or depression symptoms ( $n = 82$ ).

\* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ .

ployed rather than more well established rating scales or DSM-IV diagnostic criteria. The likelihood that such symptoms would have been mistakenly identified is slim, because evaluations were conducted by experienced geriatricians with direct observation of patients and detailed discussion with caregivers. Future studies, however, would benefit from more rigorous measurement. Second, the analyses described here are correlational and do not permit statements about the causal direction of relationships among variables. However, even such correlational data provide new information and highlight the need for more rigorous investigation of anxiety and comorbid anxiety-depression in AD. These results also suggest that even a simple evaluation of anxiety and comorbidity may provide fruitful avenues for intervention in clinical care of patients with AD.

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