

# Disruptive Behavior as a Predictor in Alzheimer Disease

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**Background:** Disruptive behavior is common in Alzheimer disease (AD). There are conflicting reports regarding its ability to predict cognitive decline, functional decline, institutionalization, and mortality.

**Objective:** To examine whether the presence of disruptive behavior has predictive value for important outcomes in AD.

**Design:** Using the Columbia University Scale for Psychopathology in Alzheimer Disease (administered every 6 months, for a total of 3438 visit-assessments and an average of 6.9 per patient), the presence of disruptive behavior (wandering, verbal outbursts, physical threats/violence, agitation/restlessness, and sundowning) was extracted and examined as a time-dependent predictor in Cox models. The models controlled for the recruitment cohort, recruitment center, informant status, sex, age, education, a comorbidity index, baseline cognitive and functional performance, and neuroleptic use.

**Setting:** Five university-based AD centers in the United States and Europe (Predictors Study).

**Participants:** Four hundred ninety-seven patients with early-stage AD (mean Folstein Mini-Mental State Examination score, 20 of 30 at entry) who were recruited and

who underwent semiannual follow-up for as long as 14 (mean, 4.4) years.

**Main Outcome Measures:** Cognitive (Columbia Mini-Mental State Examination score,  $\leq 20$  of 57 [approximate Folstein Mini-Mental State Examination score,  $\leq 10$  of 30]) and functional (Blessed Dementia Rating Scale score, parts I and II,  $\geq 10$ ) ratings, institutionalization equivalent index, and death.

**Results:** At least 1 disruptive behavioral symptom was noted in 48% of patients at baseline and in 83% at any evaluation. Their presence was associated with increased risks of cognitive decline (hazard ratio 1.45 [95% confidence interval (CI), 1.03-2.03]), functional decline (1.66 [95% CI, 1.17-2.36]), and institutionalization (1.47 [95% CI, 1.10-1.97]). Sundowning was associated with faster cognitive decline, wandering with faster functional decline and institutionalization, and agitation/restlessness with faster cognitive and functional decline. There was no association between disruptive behavior and mortality (hazard ratio, 0.94 [95% CI, 0.71-1.25]).

**Conclusion:** Disruptive behavior is very common in AD and predicts cognitive decline, functional decline, and institutionalization but not mortality.

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**D**ISRUPTIVE BEHAVIORAL symptoms (DBSs) such as agitation, verbal and physical aggression, and wandering are well-recognized symptoms in Alzheimer disease (AD), with reported frequencies ranging from 6% to 57%,<sup>1-7</sup> depending on symptom definition and the stage of illness examined. For example, in a population-based study, 40% of demented patients manifested symptoms of agitation/aggression; 18%, disinhibition; and 34%, irritability.<sup>4</sup> The presence of such features in AD is not only a source of caregiver distress<sup>8-10</sup> and financial burden (because of the need for medication treatment,

hospitalizations, and nursing home placement) but also potentially associated with important disease outcomes.

Reports examining the association between DBSs and various disease outcomes have been conflicting. Some studies have reported an association between agitation/aggression and faster cognitive decline<sup>1,10-15</sup>; between wandering/purposeless, inappropriate activities, or aggressive behavior and functional decline<sup>2,10,15</sup>; between agitation/aggression and increased risk of institutionalization<sup>16-19</sup>; and between agitation/wandering and increased mortality risk.<sup>20,21</sup> However, other reports failed to detect significant associations between disruptive behavior and cog-

niton,<sup>2,16</sup> function,<sup>15</sup> institutionalization,<sup>2</sup> or mortality.<sup>2,21</sup>

Many factors contribute to the variability in reported associations, including variability in the definitions of DBSs, inconsistent consideration of treatment with neuroleptics, use of standardized scales vs clinical evaluation, inclusion of subjects at varying stages of disease, and variable levels of participation at and duration of follow-up. Also, most previous studies considered DBSs only at a single point during the course of AD, typically at the baseline visit or, less frequently, at any point during the disease course. Because of the progressive nature of AD and the fact that neuroleptic medications can be effective in managing these symptoms, these features are not static and invariable but may fluctuate from visit to visit.<sup>5,7,22</sup> Therefore, consideration of DBSs as fixed-time variables may lead to bias toward the null.

To investigate these issues, we analyzed data from a large, multicenter cohort of patients with probable AD who were followed up from the early stages of the disease for up to 14 years, using semiannual standardized assessments of DBSs in a time-dependent fashion as predictors of important disease outcomes.

## METHODS

### PARTICIPANTS

Subjects from the Predictors Study 1 and 2 cohorts<sup>23-25</sup> were included in these analyses. For the Predictors Study 1 cohort, patients were recruited and studied at the following 3 sites in the United States: Columbia University, The Johns Hopkins University, and Harvard University. For the Predictors Study 2 cohort, the following 2 sites in the European Union were added to the 3 US sites (leading to 5 recruitment sites overall): Hospital de la Salpêtrière and the University of Thessaly. The study was approved by the appropriate local institutional review boards.

Participants were recruited from a population of subjects who were seen at outpatient clinics of these institutions that specialized in memory disorders, aging, and dementia. Subjects undergoing evaluation in these clinics were referred from other medical specialties or other neurological subspecialties or were self-referred. The inclusion and exclusion criteria and the evaluation procedures of the Predictors Study have been fully described elsewhere.<sup>23-26</sup> Briefly, patients met *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorder Association criteria for probable AD. Enrollment required a Columbia Mini-Mental State Examination (MMSE) score of at least 30 of 57 (approximately  $\geq 16$  of 30 on the Folstein MMSE<sup>27,28</sup>). The present analyses include 40 additional subjects who were recruited in the study despite a Columbia MMSE of less than 30 (removal of whom did not change the results). Exclusion criteria were parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and electroconvulsive treatments.

### EVALUATION

#### Predictors

A physician or a trained research technician administered the Columbia University Scale for Psychopathology in Alzheimer

Disease (CUSPAD)<sup>6</sup> to the informant at the initial examination and at 6-month intervals thereafter. Interrater reliabilities for DBSs between the principal CUSPAD developer and a research technician have been reported as follows:  $\kappa=0.88$  when concurrently rating a single interview and  $\kappa=0.67$  when conducting separate interviews.<sup>6</sup>

We used as predictors the following CUSPAD items (the presence of which during the last month before each interview was scored dichotomously [ie, present or absent]): (1) wandering (wandering away from home or from the caregiver), (2) verbal outbursts, (3) physical threats/violence, (4) agitation/restlessness, and (5) sundowning (increased confusion at night or during evening compared with the day [often associated with yelling, hyperkinesia, and anxiety]). Combining these items, we created the following 2 additional variables: (1) the sum of all the above symptoms (theoretical range, 0-5) and (2) the presence of any of the 5 symptoms (dichotomous).

At every 6-month visit, medications that the patients were taking were recorded. All cholinesterase inhibitors and all neuroleptics were each grouped in a single category and considered as dichotomous variables in the analyses.

A modified version<sup>24,25</sup> of the Charlson Index of Comorbidity<sup>29</sup> (hereinafter referred to as the Comorbidity Index) from the initial evaluation was also calculated.

### Outcomes

**Cognitive Outcome.** Neurologic and mental status examinations were conducted at study entry and at 6-month intervals thereafter. If patients were unable to come to the outpatient clinic for evaluation, they were visited at their homes, nursing homes, or health care facilities. The cognitive function measure used for the analysis was the Columbia MMSE (a 57-point modification and expansion of the original Folstein MMSE<sup>23-25,27,28</sup>). We used a Columbia MMSE score of at least 20 of 57 (approximately equivalent to a Folstein MMSE score of  $\leq 10$  of 30) as the cognitive end point. This cutoff was chosen because similar scores have been used as outcomes by many other studies,<sup>2,30,31</sup> including our own.<sup>24,25</sup> Exploratory analyses of neighboring end points did not change the results. Education-related differential item functioning of different Columbia MMSE components may result in biased selection of cutoffs.<sup>32</sup> This probably is less of a problem in our study, which includes only a few subjects with low levels of education. We also included education as a covariate in our analyses.

**Functional Outcome.** Functional capacity was assessed using parts I and II of the Blessed Dementia Rating Scale (BDRS),<sup>33</sup> with a range 0 to 17 and higher scores indicating worse functional status. We chose a BDRS score of at least 10 of 17 as the functional end point. The rationale for the functional cutoff was similar to the one described for the cognitive cutoff.<sup>24,25</sup> Again, exploratory analyses of neighboring BDRS end points gave similar results.

**Institutionalization.** The equivalent institutional care<sup>34</sup> that the patient was receiving was rated at each 6-month follow-up interval. This rating is the second section of a dependency scale that rates the patient's need for care (intraclass correlation coefficient, 0.73).<sup>34</sup> It summarizes the interviewer's impression, based on data from the entire study protocol, of the care the patient receives or requires, regardless of the patient's location. We used the equivalent institutional care rating of health-related facility as an end point for prediction.<sup>24,25</sup> Administration of the CUSPAD and the assessment of equivalent institutional care were performed by the same person. Although the raters were not aware of the specific study hypoth-

eses, this could still represent a source of potential bias. Because of this, we also used actual (rather than equivalent) placement in a nursing home, a retirement home, or an assisted living facility as an outcome in supplementary analyses.

**Death.** We typically learned of patients' deaths from family members or when we attempted to schedule follow-up visits. For patients who could not be contacted for follow-up or who were otherwise lost to follow-up in the US centers, death information was obtained as available through the National Death Index.

## STATISTICAL ANALYSES

To describe the course of DBSs over time, we graphed the presence of these symptoms since disease onset (as estimated by the clinicians at the first evaluation) and estimated annual changes using generalized estimating equations. The DBS sum was the dependent variable in this model. The model considered the effect of time for every evaluation (in years since the initial evaluation). A significant time effect indicates a marked change in disruptive behavioral sum scores over time.

We calculated separate Cox proportional hazards models with the following dichotomous outcomes: cognitive end point, functional end point, institutionalization, and death. Duration (in 6-month blocks) between the initial visit and either development of the outcome or last evaluation without the outcome served as the timing variable in each of these models. The main predictors in the Cox models were the DBS sum (as a continuous time-dependent covariate) and the presence of any DBS (as a dichotomous time-dependent covariate). In additional Cox models, all 5 individual DBSs (time-dependent) were simultaneously included in the analyses. Predictor values are considered from visit-assessments, not including (6-month lag) the visit-assessment when the outcome occurs. Different imputation strategies for evaluations with missing data (ie, using the value of the previous available visit or using the mean value of the previous and the following available visits) produced similar results.

Although initial Cox models were unadjusted, in subsequent ones we simultaneously controlled for the following variables: cohort (Predictors Study 1 or 2 cohort; dichotomous), recruitment center (dummy variable, with the New York center as the reference), age at intake in the study, sex, education in years, Columbia MMSE score at initial evaluation, BDRS score at initial evaluation, the Comorbidity Index (dichotomous), neuroleptic use (time dependent), and cholinesterase inhibitor use (time dependent).

## RESULTS

Overall, 497 patients with AD, approximately half from each Predictors Study cohort, were included in the study (**Table 1**). Most of the patients were recruited from the 3 centers in the United States, and patients were at relatively early stages of AD. The mean  $\pm$  SD estimated duration of illness at the time of recruitment was  $4.1 \pm 2.3$  years. The patients were, on average, well educated and in good general health. Patients were followed up from 0.1 to 14.0 years, during which time there were 3438 visit-assessments of DBSs (average, 6.9, or  $\leq 25$  per patient). During the follow-up period for each patient, missed visits were rare; fewer than 18% of patients missed more than 1 semi-annual visit and fewer than 9% missed more than 2. Follow-up was complete for 94% of the cohort, whereas only 6% of the cohort (n=27) had missing follow-up information for the year before the most updated data entry.

**Table 1. Demographic and Clinical Characteristics of Patients<sup>a</sup>**

Characteristic	Finding
Cohort 1/cohort 2	250 (50)/247 (50)
Recruitment center	
New York, New York	187 (38)
Baltimore, Maryland	128 (26)
Boston, Massachusetts	113 (23)
Paris, France	38 (8)
Larissa, Greece	31 (6)
Duration of follow-up, mean $\pm$ SD (range), y	4.4 $\pm$ 3.1 (0.1-14.0)
Age at study entry, mean $\pm$ SD (range), y	73.8 $\pm$ 8.9 (46.0-99.0)
Education, mean $\pm$ SD (range), y	13.1 $\pm$ 4.0 (0-20)
Men	197 (40)
Comorbidity Index 0/ $\geq 1$	331 (67)/166 (33)
Neuroleptic use at all evaluations	155 (31)
Cholinesterase inhibitor use at all evaluations	191 (41)
MMSE score at study entry, mean $\pm$ SD (range)	20.4 $\pm$ 3.7 (5.0-30.0)
CMMSE score at study entry, mean $\pm$ SD (range)	38.3 $\pm$ 7.4 (7.0-57.0) <sup>b</sup>
BDRS score at study entry, mean $\pm$ SD (range)	3.6 $\pm$ 2.2 (0.0-15.0) <sup>b</sup>
Equivalent institutionalization end point at baseline	39 (8) <sup>b</sup>
Cognitive end point during follow-up	198 (40)
Functional end point during follow-up	207 (42)
Equivalent institutionalization during follow-up	253 (55)
Deceased during follow-up	242 (49)

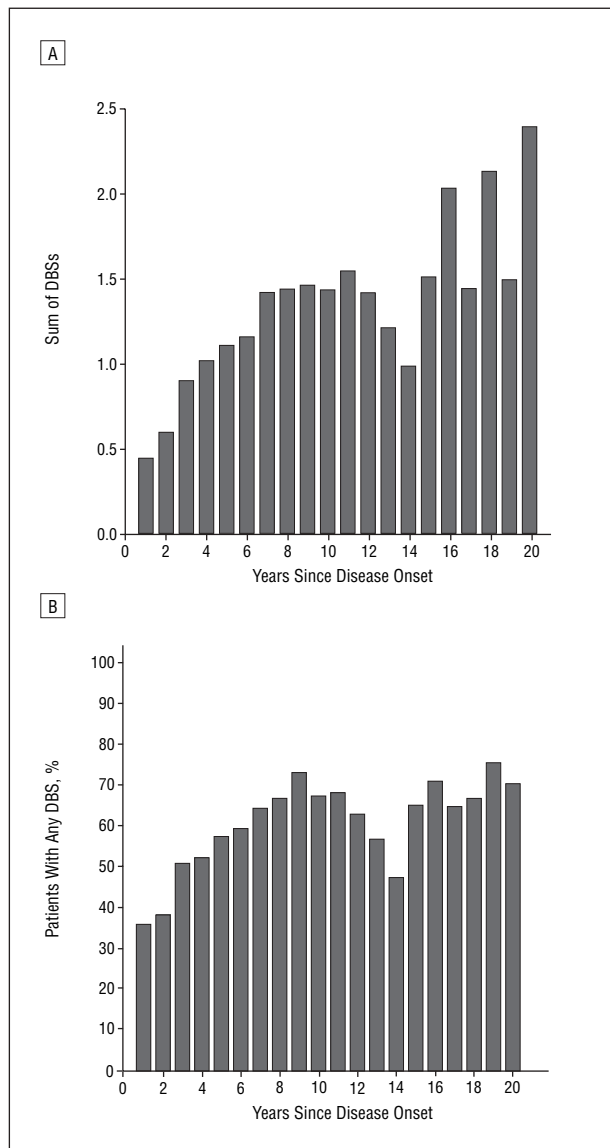
Abbreviations: BDRS, Blessed Dementia Rating Scale; CMMSE, Columbia Mini-Mental State Examination (MMSE).

<sup>a</sup>Unless otherwise indicated, data are expressed as number (percentage) of patients.

<sup>b</sup>At baseline, CMMSE values for 8 patients were below the cognitive end point, BDRS values for 8 subjects were above the functional end point, and 39 patients had reached the institutionalization end point. If a subject had already reached the end point at baseline, he or she did not contribute data to the survival analyses of the same end point but was included in the survival analyses of other end points and the mortality survival analyses.

Most of the patients developed DBSs at some point during follow-up (cumulative prevalence, 83%). Throughout the follow-up period, patients with AD manifested, on average, more than 2 DBSs (mean  $\pm$  SD,  $2.3 \pm 1.5$ ). Agitation/restlessness was the most common (manifested by approximately 3 of every 4 patients), followed by verbal outbursts and sundowning (manifested by approximately 1 of every 2 patients), whereas wandering and physical threats/violence were the least common (still noted in approximately 1 of every 3 patients). Overall, the presence of DBSs tended to increase over time (**Figure**); generalized estimating equation models indicated that the DBS sum increased by 0.07 for every year of follow-up ( $P < .001$ ).

The presence of DBSs was associated with increased risk of cognitive decline, functional decline, and institutionalization in the unadjusted and adjusted models (**Table 2**). The presence of these symptoms was associated with an approximately 1.5 times higher risk of reaching the stated outcomes. Overall, 179 patients (38%) were actually placed in a nursing home, a retirement home, or an assisted living facility. Use of actual placement as the outcome produced similar results (unadjusted DBS sum: HR, 1.31 [95% confidence interval (CI), 1.16-1.49;  $P < .001$ ]; adjusted DBS sum: HR, 1.23 [95%



**Figure.** Disruptive behavioral symptoms (DBSs) during the course of Alzheimer disease (for graphical purposes and because of the very few data points beyond 20 years after disease onset, the follow-up has been truncated to that point). A, Sum of all DBSs. B, Percentage of patients with any DBS.

CI, 1.07-1.42;  $P = .004$ )). Sundowning predicted cognitive decline, whereas wandering was the strongest predictor of functional decline and institutionalization. Agitation/restlessness was significantly associated with cognitive and functional decline (Table 2). Almost half of the patients died during the follow-up period (Table 1). Median survival from recruitment into the study was 6.6 (95% CI, 6.0-7.2) years. Disruptive behavior was not a significant predictor of mortality in any of the models (Table 2).

Neuroleptic use was associated with a higher risk of reaching the functional (HR, 1.57 [95% CI, 1.06-2.34;  $P = .02$ ]) and institutionalization (HR, 1.57 [95% CI, 1.06-2.33;  $P = .03$ ]) end points, whereas there was no association with the cognitive outcome or with mortality. Cholinesterase inhibitor use was associated with a lower risk of institutionalization (HR, 0.47 [95% CI, 0.26-0.87;  $P = .02$ ]) and mortality (HR, 0.36 [95% CI, 0.15-0.85;

$P = .02$ ]), whereas there was no association with the cognitive or the functional outcome.

Autopsy data were available for 96 patients. Of these, 93% had AD-type pathological changes (87% received the pathological diagnosis of AD and 6% had senile changes of the Alzheimer type). A pathological diagnosis of Lewy body dementia was assigned to 21% of patients (coexisting with AD-type pathological changes in all but 1 patient). Calculating the survival models only within the autopsied subsample and restricting the analyses to those with AD-type pathological changes (ie, excluding subjects with a pathological diagnosis of Lewy body dementia) did not change the associations between disruptive behavior and outcomes. When we compared patients with and without a pathological diagnosis of Lewy body dementia, there was no difference in the presence of any DBS at baseline ( $\chi^2 = 1.15$  [ $P = .28$ ]), any DBS throughout follow-up ( $\chi^2 = 0.53$  [ $P = .47$ ]), the DBS sum at baseline ( $t = -0.10$  [ $P = .92$ ]), or the DBS sum at any visit ( $t = -0.89$  [ $P = .38$ ]). Similarly, we detected no association between the presence of individual DBSs and Lewy body dementia diagnosis. Given the restricted sample size of the autopsied subjects, our power to detect an association between any DBS at baseline and a pathological diagnosis of AD vs Lewy body dementia was approximately 14%.

#### COMMENT

Disruptive behavioral symptoms were extremely common in this study; more than 80% of patients with AD manifested them at some point during follow-up. More importantly, DBSs predicted cognitive and functional decline and were associated with a higher risk of institutionalization, even after adjusting for multiple potential confounders. Although our data should provide power to detect mortality prediction effects similar in magnitude to the ones detected for the other outcomes (HR as small as 1.45 according to calculations using baseline DBS), we detected no association between disruptive behavior and mortality.

We found a notable discrepancy between the frequency of DBSs between the first and all subsequent evaluations: fewer than 60% of patients who had such symptoms at some point during the follow-up had them at the first visit. These results likely relate to an increasing prevalence of these symptoms during the course of disease and to the well-described fluctuation of these symptoms from visit to visit.<sup>5,7</sup> Therefore, our assessment of these symptoms at multiple visits rather than the usual approach of considering them only at baseline could be a major explanation for discrepancies in findings on the predictive value of these symptoms.

We confirmed the associations between DBSs and the risks of cognitive decline,<sup>1,10-15</sup> functional decline,<sup>2,10,15</sup> and institutionalization<sup>16-19</sup> noted by previous studies. Nevertheless, our results are in discordance with some previous work that failed to detect significant associations between disruptive behavior and cognition,<sup>2,16</sup> function,<sup>15</sup> or institutionalization.<sup>2</sup> As in previous studies, agitation/restlessness was predictive of cognitive<sup>1,10-15</sup> and

**Table 2. Cox Models Predicting Occurrence of the 4 Outcomes by DBSs as Time-Dependent Covariates<sup>a</sup>**

DBS	Outcome, HR (95% CI)			
	Cognitive	Functional	Institutionalization	Death
Unadjusted models				
Sum (0-5)	<b>1.31</b> (1.18-1.45)	<b>1.46</b> (1.32-1.61)	<b>1.36</b> (1.24-1.49)	1.06 (0.97-1.16)
Any (0-1)	<b>1.91</b> (1.40-2.62)	<b>2.49</b> (1.78-3.48)	<b>1.84</b> (1.40-2.41)	1.03 (0.79-1.34)
Wandering	2.09 (1.42-3.08)	1.96 (1.37-2.81)	1.99 (1.38-2.85)	
Verbal outbursts				
Physical threats/violence				
Agitation/restlessness	1.65 (1.20-2.28)	1.78 (1.27-2.47)		
Sundowning	1.57 (1.16-2.13)	1.45 (1.08-1.97)	1.49 (1.13-1.97)	
Adjusted models				
Sum (0-5)	<b>1.21</b> (1.07-1.36)	<b>1.31</b> (1.17-1.46)	<b>1.23</b> (1.11-1.37)	1.03 (0.93-1.13)
Any (0-1)	<b>1.45</b> (1.03-2.03)	<b>1.66</b> (1.17-2.36)	<b>1.47</b> (1.10-1.97)	0.94 (0.71-1.25)
Wandering		1.88 (1.27-2.78)	1.55 (1.05-2.29)	
Verbal outbursts				
Physical threats/violence				
Agitation/restlessness	1.64 (1.16-2.33)	1.49 (1.06-2.11)		
Sundowning	1.42 (1.03-1.97)			

Abbreviations: CI, confidence interval; DBS, disruptive behavioral symptom; HR, hazard ratio.

<sup>a</sup>Adjusted models simultaneously controlled for cohort, recruitment center, age, sex, education, baseline Columbia Mini-Mental State Examination score, baseline Blessed Dementia Rating Scale score, Comorbidity Index, use of cholinesterase inhibitors, and use of neuroleptics. In models considering the effect of the DBS sum or any DBS, significant HRs are given in boldface. In models that simultaneously consider all individual DBSs, only the significant associations are presented.

functional decline<sup>2,15-19</sup> outcomes. In accordance with previous reports, wandering was a significant predictor of functional decline but also the major predictor of institutionalization.<sup>10</sup> The association between DBSs and the above outcomes persisted despite controlling for medication effects. Survival in our study was similar to that in a recent report that included patients with AD of similar severity at enrollment.<sup>35</sup> Similar to some reports,<sup>2</sup> but unlike others,<sup>20</sup> we detected no significant association between disruptive behavior and survival.

In the subsample of patients who underwent autopsy, we detected no associations between DBSs and coexistence (in addition to AD) of a pathological diagnosis of Lewy body dementia. The underlying neurobiological process of disruptive behavior is far from clear and has been attributed to alterations in multiple neurotransmitter systems.<sup>36</sup> Regarding the adrenergic system, it has been shown that patients with AD who display aggressive behaviors have a markedly higher level of  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$  adrenergic receptors in the cerebellar cortex.<sup>37</sup> There is also a relative preservation of inhibitory noradrenergic neuronal input to the cerebellar cortex (tyrosine hydroxylase-positive neuronal fibers) in patients with AD who exhibit aggressive behavior.<sup>38</sup> Regarding the serotonergic system, loss of serotonin<sub>2</sub> (5-HT<sub>2</sub>) receptors in multiple cortical areas<sup>39</sup> and reduced density of 5-HT<sub>1A</sub> receptors in temporal areas<sup>40</sup> has been reported for patients with AD who manifest aggressive behavior. Decreased 5-HT receptors and 5-hydroxyindoleacetic acid levels in multiple cortical areas for aggressive patients with AD were reported in another study.<sup>41</sup> Possible involvement of the serotonin system in DBSs among patients with AD is also evidenced by a series of pharmacotherapy studies.<sup>36,42</sup> Regarding the dopaminergic system, according to one report,<sup>43</sup> patients with AD and a history of unequivocal interpersonal violence

had significantly greater neuron counts in the substantia nigra pars compacta than did nonviolent patients with AD. According to another study,<sup>44</sup> DBSs in patients with AD were associated with polymorphisms in the dopamine receptor genes: aggression was significantly more frequent in patients homozygous for the B2 genotype (B2/B2) of the *DRD1* gene. Successful treatment of aggression and agitation with dopaminergic blockers provides additional support for involvement of the dopaminergic system in the disruptive behavior of patients with AD.<sup>36,42</sup> Overall, it is also conceivable that the neurobiological changes relating to disruptive behavior may involve disturbed balance in more than 1 neurotransmitter system.

This study has limitations. The patients with AD in our study were selected from tertiary care university hospitals and specialized diagnostic and treatment centers and were well educated and extremely healthy. Also, the proportion of nonwhite patients in our sample was very small (5%). Thus, they constitute a nonrandom sample of those affected by AD, and our results have limited external validity because they might not be generalizable to population-based studies of patients with AD who are of other ethnicities or other educational and comorbidity strata. Although we used survival analyses, which take advantage of variable follow-up times, a longer average duration of follow-up with enrollment of patients at even earlier stages of the disease might have provided more complete conclusions. The DBSs were assessed as present or absent. Although the severity of these symptoms is to some extent accounted for in our models by considering medications used to treat disruptive behavior (ie, the need to treat reflects symptoms' severity according to clinical judgment), we cannot fully investigate the effects of frequency and intensity of DBSs. Medication use was coded in a dichotomous fashion for broad categories of

agents. Although we used a time-dependent approach for the medication covariate, we cannot completely take into account the potential effect of different pharmacological substances, different doses, or alterations occurring in intervals shorter than 6 months. Finally, the absence of pathological correlates of DBSs may partially stem from the qualitative pathological measures we have available and from the limited power of the autopsy sample.

Confidence in our findings is strengthened by several factors. This is, to our knowledge, one of the largest studies of its kind examining the issue of disruptive behavior in AD, supplying enough power for detection and more precise calculation of effects of interest and ability to control potential confounders. Inclusion of population from 2 European centers improves the generalizability of the findings. Clinical diagnosis and follow-up were performed by physicians with specific expertise in dementia and were based on the uniform application of widely accepted criteria via consensus diagnostic conference procedures. The clinical diagnosis of AD has been confirmed in a high proportion of those who underwent postmortem evaluation (93%).<sup>23,25</sup> The patients were followed up prospectively, which eliminates the potential biases inherent in deriving information from retrospective medical chart reviews. Evaluations were performed semiannually, which provides multiple assessments of DBSs and therefore permits more accurate coefficient calculations. They were also considered in a time-dependent fashion. Our cohort had a very high rate of follow-up participation with very few missing data. Clinical signs of interest were ascertained and coded in a standardized fashion at each visit. Most previous reports studied more impaired patients with AD, capturing the part of the disease course corresponding to more advanced stages. Patients with AD were included from relatively early stages so that the cohort captures most of the range of progression over time. Finally, we took medication administration into account in a time-dependent manner, which provides higher confidence that the occurrence of outcomes of interest in the present study is strictly related to the presence of DBSs rather than treatment for them.

Prognosis is a standard part of a medical evaluation, and knowledge of prognostic indicators is important information to practitioners, patients, and families. These data provide a basis for expanding our understanding of disruptive behavior as a predictor in the course of AD. The underlying pathophysiological substrate of the associations between such neuropsychiatric features and clinical outcomes remains to be explored.

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