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Sleep Disturbance in Dementia with Lewy Bodies and Alzheimer's Disease: A Multicenter Analysis

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Key Words
Dementia with Lewy bodies · Alzheimer's disease · Sleep · Neuropsychiatric Inventory Questionnaire

Abstract
Background/Aims: Evidence suggests that patients with dementia with Lewy bodies (DLB) may have more nocturnal sleep disturbance than patients with Alzheimer's disease (AD). We sought to confirm such observations using a large, prospectively collected, standardized, multicenter-derived database, i.e. the National Alzheimer's Coordinating Center Uniform Data Set. ***Methods:*** Nocturnal sleep disturbance (NSD) data, as characterized by the Neuropsychiatric Inventory Questionnaire (NPI-Q), were derived from 4,531 patients collected between September 2005 and November 2008 from 32 National Institute on Aging participating AD centers. Patient and informant characteristics were compared between those with and without NSD by dementia diagnosis (DLB and probable AD). Finally, a logistic regression model was created to quantify the association between NSD status and diagnosis while adjusting for these patient/informant characteristics, as well as center. ***Results:*** NSD was more frequent in clinically diagnosed DLB relative to clinically diagnosed AD (odds ratio = 2.93, 95% confidence interval = 2.22–3.86). These results were independent from the gender of the patient or informant, whether the informant lived with the patient, and other patient characteristics, such as dementia severity, depressive symptoms, and NPI-Q-derived measures of hallucinations, delusions, agitation and apathy. In AD, but not DLB, patients, NSD was associated with more advanced disease. Comorbidity of NSD with hallucinations, agitation and apathy was higher in DLB than in AD. There was also evidence that the percentage of DLB cases with NSD showed wide variation across centers. ***Conclusion:*** As defined by the NPI-Q, endorsement of the nocturnal behavior item by informants is more likely in patients with DLB when compared to AD, even after the adjustment of key patient/informant characteristics.

Introduction

Sleep disturbance occurs in many forms of dementia; however, it is possible that certain forms of dementia may be relatively more likely to be associated with disturbed sleep. For example, the Third International Consensus

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Conference definition of dementia with Lewy bodies (DLB) [1] indicates that rapid eye movement (REM) sleep behavior disorder (RBD) may be important in defining this condition. Although patients with Alzheimer's disease (AD) have also been known to have disrupted sleep [2] and may experience changes in circadian rhythms [2, 3], few studies have compared the presence of disturbed sleep between these two neurodegenerative conditions. In this study, we report on a comparison of informant-reported nighttime behaviors in secondary data analyses of a large national database of well-characterized patients with AD and DLB using the National Institute on Aging (NIA) Uniform Data Set (UDS).

Methods

Data in this study were derived from the UDS covering the period of September 2005 to November 2008 maintained by the National Alzheimer's Coordinating Center (NACC) located at the University of Washington under the auspices of the NIA. Development of the UDS has been described elsewhere [4, 5] but, in brief, consists of a deidentified, web-based, relational database, which serves as a repository for data collected by the 32 NIA-funded AD centers. Access to the NACC UDS database is available to all interested researchers associated with an NIA-sponsored AD research center via formal request to the NACC Steering Committee through the NACC website (https://www.alz.washington.edu; see Beekly et al. [4] and Lau et al. [6] for further information).

All patients or their proxies provided informed consent through an Institutional Review Board-approved protocol at each site. All patients entered in the UDS received a physician-based clinical diagnosis. Autopsy verification is pursued in many centers as a part of the NACC data collection but was not incorporated into the analyses presented here. As is customary of patients encountered in clinics focusing on dementias, a broad range of diagnoses are considered. In this study, analyses were limited to cases with a diagnosis of DLB or probable AD. Clinical diagnosis for each of these conditions followed consensus-based definitions and criteria [1, 7, 8]. Additional data employed in the study were patient and informant demographics (e.g. gender, age, and education), the 15-item form of the Geriatric Depression Scale (GDS) [9] and the Mini-Mental State Exam [10]. The Clinical Dementia Rating (CDR) [11] was used to rate the severity of each patient's dementia, calculated as the sum of boxes (SOB). Finally, we relied upon an informant-derived measure dealing with behavioral syndromes common in dementia patients, i.e. the Neuropsychiatric Inventory Questionnaire (NPI-Q) [12, 13], which has been validated in AD patients, though not necessarily DLB patients [13]. The NPI-Q requires that the informant report on the patient's behaviors during the preceding month, which also entails severity, and is included as a part of the UDS. As described on the NACC website, one of the aims of the UDS is to ensure high-quality assurance for all data collected, and to that end, the NPI-Q is completed by a trained health professional via informant interview. In some cases, adult children of the patients served as informants. We focused on several specific items on the NPI-Q, including the presence or absence of agitation/aggression, hallucinations, delusions, nighttime behaviors, apathy, and depressed mood. The nighttime behavior item was: 'Does the patient awaken you at night, rise too early in the morning, or take excessive naps during the day?', which could be answered with 'yes' or 'no' (see Cummings et al. [12] for specific wording of other NPI-Q items). Informant responses to this item were categorized as positive or negative for nighttime sleep disturbance (NSD). Although clinical diagnoses in the UDS are based on expert consensus at each participating center, the possibility exists that information related to sleep gathered on the NPI-Q may also have been used diagnostically at some centers.

Statistical Analyses

Descriptive statistics were calculated for patient and informant demographics and neurobehavioral instruments (e.g. Mini-Mental State Exam, NPI-Q, GDS) by diagnosis and NSD status. Continuous variables were summarized by means ± 1 standard deviation and categorical variables by percentages. Comparisons within diagnosis groups (probable AD and DLB) by NSD status were performed via the Wilcoxon rank sum or Pearson χ^2 tests for continuous and categorical variables, respectively. The unadjusted p values from these comparisons were calculated, but the Bonferroni adjustment to the type I error (0.05/34 = 0.0015) may be applied to account for multiple comparisons.

To quantify the association between diagnosis and NSD, a multivariate logistic regression model was developed using data from all 32 centers. This model also accounted for patient characteristics (age, gender, race, marital status), informant gender, NPI-Q items (depression, hallucinations, delusions, agitation, apathy), and CDR SOB. Because it was of interest to investigate center differences, center ID was included as an adjustment variable and not accounted for as a random effect. All covariates, except CDR SOB, were categorical and modeled as a series of binary variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to summarize the model. The robustness of these estimates was assessed by refitting the model on data derived from patients that were living with others. All analyses were performed using R version 2.11 [14].

Results

As of November 1, 2008, 4,444 patients with a primary diagnosis of probable AD and 354 patients with a primary diagnosis of DLB were available for analysis. Of these patients, 4,531 (94%) had complete NPI-Q data and served as the basis for the current work. DLB (4.2%) and AD (5.7%) patients did not differ in the proportions of missing NPI-Q data ($\chi^2 = 1.29$, p = 0.26, d.f. = 1). However, those with missing NPI-Q data were significantly older (78.8 ± 9.7 vs. 76.1 ± 9.3 years, t = 4.60, $p < 0.0001$, d.f. = 4,796) and more likely to be women (62.6 vs. 37.5%, $\chi^2 = 6.30$, p = 0.01, d.f. = 1). Among those with complete NPI-Q data, there were 4,192 AD (1,810 men and 2,382

women) and 339 DLB (244 men and 95 women) patients, respectively. DLB patients were more likely to be men (72.0% of DLB patients were male, whereas only 43.2% of AD patients were male, $\chi^2 = 104.96$, $p < 0.0001$, d.f. = 1). AD patients were significantly older than DLB patients (76.2 ± 9.4 vs. 74.0 ± 7.8 years, $t = 4.20$, $p < 0.0001$, d.f. = 4,529). The presence of NSD was significantly higher among DLB patients relative to probable AD patients (63.1 vs. 26.6%, $\chi^2 = 201.9$, d.f. = 1, $p < 0.0001$).

Table 1 compares patient and informant characteristics for patients with and without NSD by diagnosis. Results suggest that among probable AD patients, those with NSD were more likely to be older and black, whereas among DLB patients, those with NSD were more likely to be male and married. Few other patient or informant characteristics appeared to distinguish diagnostic groups having or not having NSD.

Differences among centers were apparent. Of the 13 centers reporting 9 or more DLB cases, the presence of NSD ranged from 22.2 to 80.0%. The frequencies of NSD in all centers and their 95% bootstrapped CI are presented in figure 1 and suggest that, along with wide CI among some centers contributing only a small number of cases, there was considerable variation in the presence of NSD in DLB by center, relative to the presence of NSD in AD.

Table 2 examines the extent to which dementia severity and depressive symptoms may have differentiated patients with informant-reported NSD from those without NSD. The CDR SOB was significantly higher in AD patients with informant-reported NSD, but this relationship was not seen in DLB, implying that in AD patients NSD may be a late-stage, rather than early-stage, disease correlate. Higher depression scores were also associated with NSD in AD, but not DLB, patients.

Informant-reported NSD was also associated with several other key aspects of behavioral disturbance on the NPI-Q, including delusions, hallucinations, agitation and apathy (table 3). These informant-reported phenomena were associated with informant-reported NSD in both DLB and AD. It is noteworthy that the comorbidities between these phenomena were higher in DLB, relative to AD patients, implying that such behavioral manifestations are more likely to represent an overlapping, common phenotype in the former, relative to the latter. The nonmotor symptoms of DLB may thus constitute a more recognizable constellation of behaviors than they do in AD, where such phenomena may be more likely to occur in a somewhat more isolated fashion.

The regression summary (OR and 95% CI) is presented in table 4. Because there were fewer cases missing NPI-Q items relative to missing data with the GDS, we included the NPI-Q depressed mood item in this model. These data suggested that although older age, male gender, black race, CDR SOB, and NPI-Q-derived assessments of depressive symptoms, hallucinations, delusions, agitation and apathy were associated with NSD, the presence of DLB diagnosis was by far the strongest predictor (OR = 2.93, 95% CI = 2.22–3.86). Significant differences were also noted among a few of the centers. Data were virtually identical when cases living alone were excluded (OR for diagnosis = 3.18, 95% CI = 2.39–4.23), suggesting that inclusion of those cases did not influence this association.

Discussion

These data indicate that substantial proportions of DLB and AD patients experience some aspect of disturbed sleep, with the former showing an apparent presence well over twice that of the latter. The data thus confirm what preliminary analyses in much smaller samples of such patients from particular sites [15–19] and of patients with more generally defined parkinsonism [20] have demonstrated previously. Patients with DLB are more likely to suffer from NSD than patients with AD. The neurobiological substrates for the preferential association of sleep disturbance with synucleinopathies versus amyloidopathies remain speculative, but are thought to involve the primacy of brainstem degeneration in parkinsonian-like conditions [17, 21, 22]. Such deterioration may impact upon nuclei such as the pedunculopontine nucleus, the sublaterodorsal nucleus, the magnocellular reticular formation, or other structures and their afferent/efferent projections, which ultimately lead to dysregulation of normal REM sleep atonia [21, 23]. Among the AD patients, but not the DLB patients, NSD was more likely to be associated with more advanced disease (i.e., CDR). This is consistent with the observation that sleep disturbance may be one of the earliest signs of a synucleinopathy [24] and one that remains prominent throughout disease course or may even decrease [25], whereas in AD it may be a sign of late-stage disease [26, 27].

Hypersomnolence as captured by a positive response to the phrase on the NPI-Q 'take excessive naps during the day' could reflect a circadian dysrhythmia, coexistent obstructive and/or central sleep apnea syndrome, restless legs syndrome/periodic limb movement disorder, a narcolepsy-like disorder, another primary sleep disorder, or an effect of medications. It may also reflect apathy, which

Table 1. Patient and informant characteristics of the NACC UDS database by diagnosis and NPI-Q-assessed NSD

	DLB (n = 339)				Probable AD (n = 4,192)			
	without NSD (n = 125)	with NSD (n = 214)	test statistic	p value	without NSD (n = 3,077)	with NSD (n = 1,115)	test statistic	p value
Patient characteristics								
Age group			$\chi^2_6 = 9.8$	0.133			$\chi^2_6 = 13.4$	0.038
<60	4	5			6	6		
60–64	10	7			6	5		
65–69	15	13			9	8		
70–74	15	29			16	14		
75–79	28	23			23	24		
80–84	17	15			23	22		
>84	10	8			17	21		
Gender			$\chi^2_1 = 5.1$	0.025			$\chi^2_1 = 3.5$	0.061
Male	65	76			42	46		
Female	35	24			58	54		
Education			$\chi^2_3 = 4.6$	0.205			$\chi^2_3 = 4.1$	0.253
<High school	7	8			10	12		
High school	37	26			31	32		
College	30	37			38	35		
Graduate	26	29			21	21		
Race/ethnicity			$\chi^2_3 = 2.4$	0.493			$\chi^2_3 = 59$	<0.001
Non-Hispanic White	88	90			78	69		
Non-Hispanic Black	4	6			11	20		
Non-Hispanic other	2	1			2	3		
Hispanic	6	3			8	8		
Living situation			$\chi^2_1 = 10.5$	0.001			$\chi^2_1 = 5.1$	0.024
Alone	10	2			15	13		
With others	90	98			85	87		
Marital status			$\chi^2_2 = 5.8$	0.056			$\chi^2_2 = 10$	0.007
Married/living with partner	76	86			66	61		
Not currently married	22	13			31	36		
Never married/other	2	1			3	2		
Informant characteristics								
Relationship with patient			$\chi^2_1 = 3.9$	0.047			$\chi^2_1 = 5.3$	0.021
Spouse/partner	69	79			58	54		
Non-spouse/partner	31	21			42	46		
Living with patient			$\chi^2_1 = 6.3$	0.012			$\chi^2_1 = 3.5$	0.060
No	26	15			32	29		
Yes	74	85			68	71		
Gender			$\chi^2_1 = 4.3$	0.039			$\chi^2_1 = 11$	0.001
Male	23	14			34	29		
Female	77	86			66	71		
Education			$\chi^2_3 = 1.8$	0.608			$\chi^2_3 = 1.0$	0.796
<High school	3	2			2	2		
High school	23	30			24	24		
College	50	45			46	48		
Graduate	24	23			28	26		
Reliability			$\chi^2_1 = 0.3$	0.571			$\chi^2_1 = 0.4$	0.508
No	98	99			97	97		
Yes	2	1			3	3		

Variables are summarized as percentages and comparisons within diagnosis by NSD were computed using Pearson's test. A 'yes' response on 'reliability' refers to cases for whom credibility of the informant may be questionable.

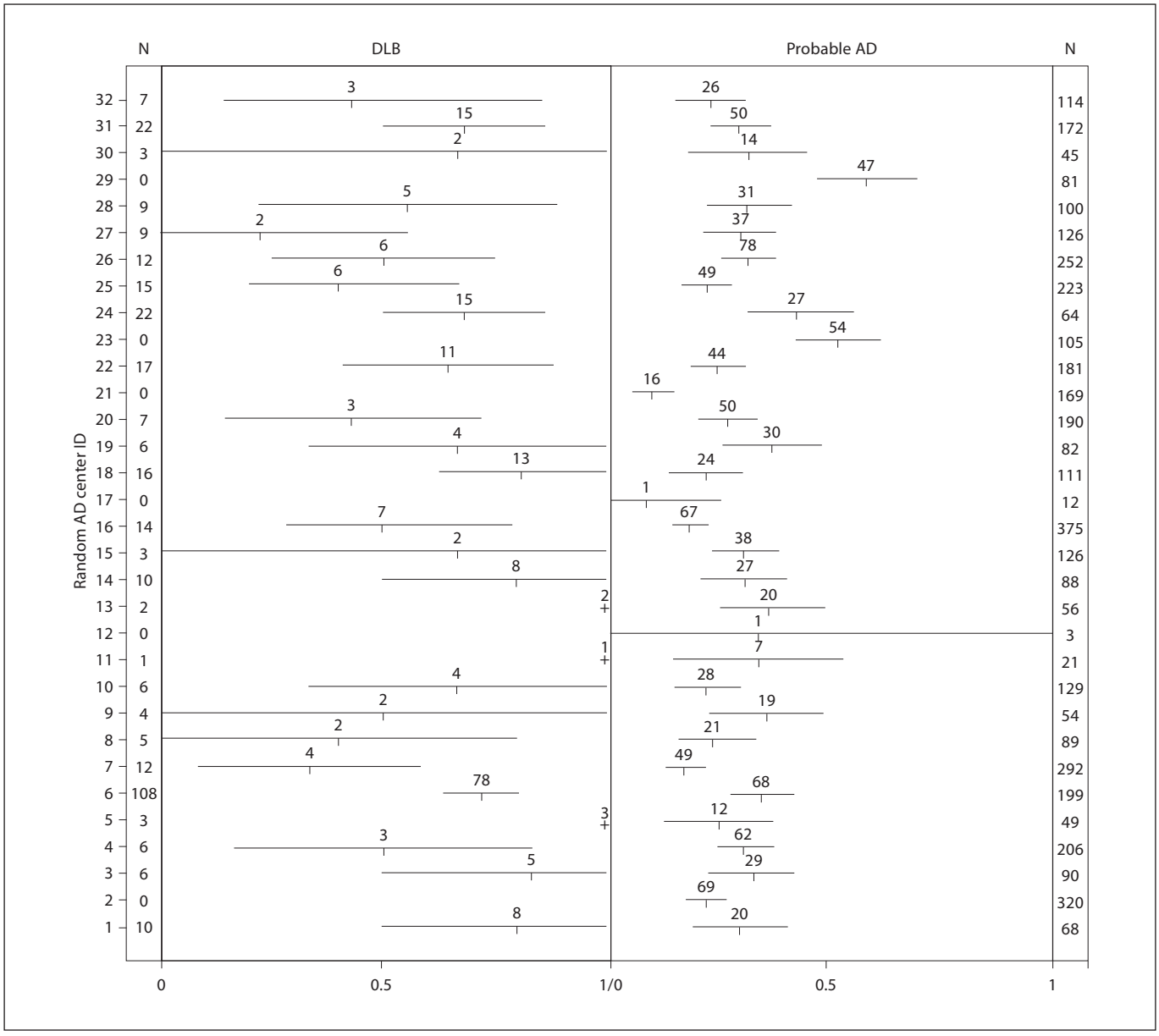

Fig. 1. Proportion of subjects with NPI-Q-assessed NSD by diagnosis and by center. Intervals represent 95% bootstrapped CI and values above each interval correspond to the number of subjects with NSD at the specific center. The total number of subjects with DLB (or probable AD) for each center are denoted in column N, respectively.

may overlap with sleepiness to some degree. The frequencies of these various sleep disorders among DLB and AD patients are not well characterized, but these warrant further study, as they could be differentially expressed in DLB versus AD and provide diagnostic clues. Furthermore, as reflected by endorsement of frequent napping, hypersomnolence could contribute to the fluctuations in cognition and/or arousal which are considered a core feature of DLB [17].

Weaknesses of the current analyses include the fact that the UDS database essentially represents a convenience sample of patients presenting at academic AD centers, lack of autopsy verification of clinical diagnosis, lack of control over medication usage and daytime activity

Table 2. Disease severity and depressive symptoms in relation to NPI-Q-assessed NSD in DLB and AD patients

	DLB (n = 339)				Probable AD (n = 4,192)			
	without NSD (n = 125)	with NSD (n = 214)	test statistic	p value	without NSD (n = 3,077)	with NSD (n = 1,115)	test statistic	p value
MMSE score (mean ± 1 SD)	23.0 ± 16.9	24.0 ± 16.5	$F_{1, 337} = 0.29$	0.59	21.6 ± 14.4	21.7 ± 16.7	$F_{1, 4,190} = 4.3$	0.037
CDR SOB	6.9 ± 5.1	7.2 ± 4.5	$F_{1, 337} = 2.0$	0.15	6.7 ± 4.3	8.0 ± 4.7	$F_{1, 4,190} = 70$	<0.001
NPI-Q depression item, %	45	52	$\chi^2_1 = 1.8$	0.18	33	48	$\chi^2_1 = 74$	<0.001
GDS	4.3 ± 3.4	4.5 ± 3.3	$F_{1, 283} = 0.63$	0.43	2.3 ± 2.5	2.7 ± 2.7	$F_{1, 3,653} = 18$	<0.001

MMSE = Mini-Mental State Exam. Continuous variables are summarized with mean ± 1 standard deviation and categorical variables by percentages. p values represent comparisons using the Wilcoxon (for continuous variables) or Pearson's test (for categorical variables). For GDS: 3,655 (87%) and 285 (84%) responses noted for probable AD and DLB, respectively.

Table 3. Comorbidity of NPI-Q-assessed NSD with hallucinations, delusions, agitation and apathy in DLB and probable AD

	DLB (n = 339)	Probable AD (n = 4,192)	Test statistic	p value
Hallucinations	31.0	4.9	$\chi^2_1 = 333.2$	<0.001
Delusions	19.2	7.5	$\chi^2_1 = 55.5$	<0.001
Agitation	28.0	13.4	$\chi^2_1 = 54.5$	<0.001
Apathy	47.5	15.2	$\chi^2_1 = 226.0$	<0.001

Informants may have endorsed one or more NPI-Q items. Proportions represent the percentages of patients for each diagnostic group (DLB or AD) with NSD and a particular comorbidity (hallucinations, delusions, agitation, and apathy). Pearson χ^2 and p values represent the comparison between DLB and AD.

level, as well as the limitation of the NPI-Q as the sole source of information regarding nocturnal behavior. There are many disadvantages of the NPI-Q nighttime behavior item. The NPI-Q was selected for inclusion in the UDS because of its demonstrated utility and validity in gathering data on a wide variety of behavioral syndromes associated with dementia [12], but its use was not driven specifically by an interest in sleep or sleep behavior. We could locate only one very preliminary study reporting convergent validity of the NPI-Q sleep item with other sleep questions, which themselves were summarized globally into a single score [28]. The fundamental limitation of the item is that it consists of three separate, undifferentiated components (nocturnal awakenings, arising too early in the morning, or excessive daytime napping), which may or may not occur concurrently in dementia patients [2, 29–31]. (The final component, daytime sleepiness, arguably does not even constitute a 'nighttime' behavior, though one might infer that it could represent an outcome of poor sleep at night [32, 33]. Our finding that informant-endorsed apathy on the NPI-Q also overlapped with the nighttime behavior item further suggests possible overlap with daytime sleepiness). Furthermore, none of these three components implicit within the single question specifically target dream enactment behaviors during REM (so-called 'active sleep') that constitute one of the suggestive criteria (i.e., the behavioral manifestation of RBD) for DLB diagnosis [1]. Such an omission could represent a 'false negative'.

Of consequence in the current work is that the more likely presence of NSD in DLB relative to AD was a robust finding. It occurred independently from the patient's gender or the informant's gender. It also occurred regardless of whether the informant lived with or was married to the patient. Various centers also differed in the presence of NSD at their respective sites, particularly for DLB cases. Among the 13 centers encountering 9 or more DLB cases, informant-endorsed NSD ranged from as low as 22% (center 27) to as high as 81% (center 18) (fig. 1), whereas the range for NSD in AD cases among those same centers was about half of that (as low as 17% for center 7 to as high as 42% for center 24). Informant endorsement variability can be interpreted in several different ways. It is possible that DLB patients at certain centers had more disturbed sleep and that the informant reports reflected that fact. The UDS did not collect data on household sleeping arrangements, which makes it impossible to know whether some informants might not be missing sleep disturbance, for example, by not sleeping in the same bedroom as the patients. Data such as these might enhance the understanding of these apparent site differences. However, this type of influence would not be expected to operate systematically at different sites and vary systematically between

Table 4. Multivariate logistic regression model of predictors of NPI-Q-assessed NSD

		OR	95% CI	p value
Age group	<60	1.00	–	–
	60–64	1.01	0.66–1.54	0.972
	65–69	1.13	0.76–1.66	0.550
	70–74	1.27	0.89–1.80	0.191
	75–79	1.39	0.99–1.95	0.061
	80–84	1.40	0.99–1.98	0.055
	>84	1.64	1.14–2.35	0.007
Patient gender	Male	1.00	–	–
	Female	0.66	0.54–0.80	<0.0001
Informant gender	Male	1.00	–	–
	Female	0.93	0.76–1.13	0.451
Race	Non-Hispanic White	1.00	–	–
	Non-Hispanic Black	1.39	1.10–1.74	0.005
	Non-Hispanic other	1.05	0.65–1.71	0.835
	Hispanic	0.98	0.73–1.32	0.902
NPI-Q depression	no	1.00	–	–
	yes	1.49	1.28–1.74	<0.0001
Diagnosis	Probable AD	1.00	–	–
	DLB	2.93	2.22–3.86	<0.0001
CDR SOB		1.03	1.01–1.05	0.003
NPI-Q: hallucinations	no	1.00	–	–
	yes	2.35	1.88–2.94	<0.0001
NPI-Q: delusions	no	1.00	–	–
	yes	1.25	1.04–1.51	0.020
NPI-Q: agitation	no	1.00	–	–
	yes	1.59	1.36–1.86	<0.0001
NPI-Q: apathy	no	1.00	–	–
	yes	1.58	1.36–1.84	<0.0001
Marital status				
Married		1.00	–	–
Not currently married		1.21	1.00–1.48	0.053
Never married/other		1.13	0.69–1.86	0.619
NACC center number	6	1.00	–	–
	1	0.76	0.42–1.37	0.365
	2	0.44	0.30–0.65	<0.0001
	3	0.73	0.43–1.23	0.238
	4	0.74	0.49–1.13	0.166
	5	0.84	0.43–1.67	0.628
	7	0.40	0.26–0.61	<0.0001
	8	0.45	0.25–0.81	0.008
	9	0.94	0.50–1.77	0.857
	10	0.63	0.38–1.03	0.067
	11	0.88	0.34–2.31	0.796
	12	1.12	0.08–15.27	0.934
	13	0.90	0.48–1.69	0.736
	14	0.94	0.56–1.59	0.826
	15	0.80	0.49–1.30	0.364
	16	0.49	0.34–0.72	0.001
	17	0.16	0.02–1.33	0.090
	18	0.80	0.49–1.30	0.368
	19	1.09	0.64–1.86	0.739
	20	0.62	0.40–0.95	0.027
	21	0.24	0.13–0.44	<0.0001
	22	0.63	0.41–0.97	0.038
	23	1.34	0.80–2.24	0.264
	24	1.24	0.72–2.12	0.437
	25	0.66	0.44–1.01	0.055
	26	0.92	0.63–1.35	0.666
	27	0.52	0.32–0.85	0.009
	28	1.05	0.63–1.73	0.864
	29	2.56	1.46–4.49	0.001
	30	0.79	0.19–3.21	0.741
	31	0.87	0.57–1.32	0.500
	32	0.57	0.32–1.01	0.053

CDR SOB represents each unit increase in SOB. Center 6 was used as reference group because it contained the largest number of DLB patients.

DLB and AD cases. On the other hand, the possibility exists that different centers might implicitly weight the informant's report of NSD differently when establishing a diagnosis of DLB. Although RBD is now acknowledged to represent a strongly suggestive feature of DLB [1], it is unclear how various centers may view these data as crucial or not crucial for establishing this differential diagnosis relative to AD. If the latter situation even represents the most remote possibility, it certainly draws attention to the importance of an independent and more detailed assessment of sleep/wake function in the evaluation of all dementia patients, perhaps even physiologically. For example, we have recently noted that phasic muscle activity in limbs [34], recorded from a single REM sleep period, is a useful objective physiologic marker to differentiate individuals with a history of RBD from controls, even when dream enactment behaviors were not detected when sleeping in the laboratory for a single night [35]. Such electromyographic activity, labeled the phasic electromyographic metric (PEM), may provide objective verification of the phenomena that informants are providing here via the NPI-Q. Such measures may also be particularly informative by providing insights into the underlying neurodegenerative disorder in the clinical setting of mild cognitive impairment when the other more 'classic' features of AD and DLB have not yet become manifest.

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Disclosure Statement

Dr. Bliwise has served on the Advisory Board for Takeda Pharmaceuticals and has been on the Speaker's Bureau for Takeda Pharmaceuticals and Boehringer-Ingelheim. Mr. Mercaldo reports no disclosures. Dr. Avidan has served on the Advisory Board for Takeda Pharmaceuticals and has been on the Speaker's Bureau for Takeda Pharmaceuticals, Sanovian, Cephalon, and Pfizer. Dr. Boeve has received grant support from Myriad Pharmaceuticals and honoraria from General Electric Healthcare. Ms. Greer reports no disclosures. Dr. Kukull reports no disclosures.

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