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Impact of Dementia-Related Behavioral Symptoms on Healthcare Resource Use and Caregiver Burden: Real-World Data from Europe and the United States

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Abstract.
Background: Dementia is commonly accompanied by neurobehavioral symptoms; however, the relationship between such symptoms and health-related outcomes is unclear.
Objective: To investigate the impact of specific neurobehavioral symptoms in dementia on healthcare resource use (HCRU), patient quality of life (QoL), and caregiver burden.
Methods: Data were taken from the 2015/16 Adelphi Real World Dementia Disease Specific Programme™, a point-in-time survey of physicians and their consulting dementia patients. Multiple regression analyses were used to examine associations between patient symptom groups and health-related outcomes.
Results: Each patient symptom group of interest (patients with agitation/aggression and related symptoms [AARS] with psychosis, patients with AARS without psychosis, and patients with other behavioral symptoms) had a positive association with HCRU variables (i.e., HCRU was greater), a negative association with proxy measures of patient QoL (i.e., QoL was decreased), and a positive association with caregiver burden (i.e., burden was greater) compared with patients with no behavioral symptoms (control group). The magnitude of effect was generally greatest in patients with AARS with psychosis. Regression analysis covariates that were found to be most often significantly related to the outcomes were dementia severity and the patients' living situation (i.e., whether they were in nursing homes or living in the community).
Conclusion: Combinations of behavioral symptoms, particularly involving AARS plus psychosis, may have a detrimental impact on health-related outcomes such as HCRU, patient QoL, and caregiver burden in dementia. Our results have implications for intervention development in patients who report clusters of symptoms and caregivers, and for identifying at-risk individuals.

Keywords: Aggression, agitation, behavioral symptoms, burden, caregivers, cognitive impairment, dementia, healthcare resource use, quality of life

INTRODUCTION

Dementia means the inability to function independently in everyday activities after significant cognitive decline, the most common etiology of which is Alzheimer's disease (AD). Around 50 million people have dementia worldwide and it is currently the fifth leading cause of death [1]. The global prevalence of dementia is projected to reach 82 million in 2030 and 152 million in 2050 [1]. Dementia mainly affects older people; however, it is not

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considered a normal part of aging. It is one of the most disabling conditions worldwide and the disease burden increases with the aging global population. Dementia has significant social and economic implications: In 2015, the total global societal cost was estimated at US$ 818 billion, equivalent to 1.1% of global gross domestic product [1]. There is currently no available treatment to cure or slow the progressive course of dementia, although several treatments are being investigated in clinical trials.

The main symptom of dementia is the progressive impairment in cognitive function, affecting an individual's memory, thinking, orientation, comprehension, learning, language, and judgement. Cognitive impairment (CI) is commonly accompanied by neurobehavioral symptoms, which can include depression or dysphoria (a profound sense of unease or dissatisfaction), anxiety, apathy, psychosis, irritability, aggression, impulsivity, and sleep disorders [2–4]. Neurobehavioral symptoms affect nearly all patients living with dementia at some point in their disease course [3, 5, 6] and increase as the disease progresses [6].

Three European studies (the Maastricht Study of Behavior in Dementia, the Réseaux Alzheimer Français, and the European AD Consortium [EADC]) provided details of the most common neurobehavioral symptoms in dementia. Apathy was the most common abnormality (observed in 48–64% of patients across the studies), followed by depression (37–57%) and anxiety (34–46%). Agitation and irritability were also common symptoms [2, 5, 7, 8].

Neurobehavioral symptoms are a major challenge and drive a large proportion of the social burden of dementia, for both patients and their caregivers; and thus they are important targets for intervention [4, 9, 10]. These symptoms have become the focus of research in recent years [2, 4] and are now recognized to be as clinically significant as cognitive decline [9].

Some of this research has focused on groups of symptoms. A consensus review paper from the EADC suggested there was some evidence for groups of correlated symptoms which could be studied together [2]; however, most studies do not use symptom groups but study individual symptoms or total symptom scores. van der Linde et al. (2013) carried out a literature review including 62 studies in order to identify clusters or factors of behavioral and psychological symptoms in dementia [4]. The studies investigating symptom groups showed relatively consistent results, i.e., generally the included studies used the following symptom groups: affective symptoms (including depression and anxiety), psychosis (including delusions and hallucinations), hyperactivity (including irritability and aggression), and euphoria. The authors suggested symptom groups may differ in their associations, treatment, and underlying biology. Of interest, no clear differences were seen between studies of populations with different levels of cognitive function, i.e., mild CI to moderate/severe dementia [4]. In agreement with this, Zuidema et al. (2007) found that groups of neuropsychiatric symptoms were relatively stable across dementia stages in Dutch nursing home residents [11]. Furthermore, two studies investigating co-occurrence of symptoms using factor analysis found that the factor structure was largely consistent across non-dementia groups (patients with mild CI subtypes and with mild to moderate CI) and was similar, although with weaker associations, to that seen in a population with dementia [12, 13]. Yet, other studies are in disagreement with these findings, suggesting that greater CI or dementia severity is associated with higher rates of neurobehavioral symptoms [6, 14, 15].

Studying symptom groups allows similar symptoms to be studied together, which might strengthen results and may point to differences in their etiology and treatment [4]. However, little research has investigated the effect of these specific symptom groups on health-related outcomes, particularly healthcare resource use (HCRU) and patient quality of life (QoL).

In light of the previous research, the primary aim of the current study was to investigate the impact of neurobehavioral symptoms (namely agitation/aggression and related symptoms [AARS]) in dementia on health-related outcomes of HCRU, patient QoL, and caregiver burden.

MATERIALS AND METHODS

Data collection

Data were taken from the 2015/16 Adelphi Real World Dementia Disease Specific Programme (DSP)™. DSPs are real-world, point-in-time surveys of physicians and their consulting patients, which have a validated methodology [16, 17]. Physicians from a range of locations across Europe (France, Germany, Italy, Spain, and the United Kingdom [UK]) and the United States (US) were identified from publicly available lists of healthcare professionals and invited to participate in the DSP.

Primary care physicians (PCPs) and physicians with a specialty as geriatricians, neurologists, psycho-geriatricians, psychiatrists, neuropsychiatrists, or specialists in neurodegenerative diseases were eligible for this analysis. To be included, physicians were required to have qualified between 1979 and 2012 and be responsible for treatment decisions for patients with CI. Specialist physicians were required to see ≥ 10 patients and PCPs ≥ 5 patients with CI in a typical week. The DSP sample included patients who were aged ≥ 30 years with a diagnosis ranging from very mild CI to AD. Patients with dementia of purely vascular origin or due to environmental factors (e.g., traumatic head injury or alcoholism) were excluded.

Physicians were asked to complete a record form for the next 10 consecutively consulting patients with CI: Information recorded included demographics and clinical characteristics, presence of symptoms/behaviors (AARS, psychosis, or other behavioral symptoms) and their combinations, and results from validated measures of HCRU, QoL, and caregiver burden (described in detail below). Information was obtained retrospectively by reviewing patients' medical records; there was no time limit on how far back the physician could look.

Analysis

Multiple regression analyses were used to examine associations between patient symptom groups and various health-related outcomes. The following symptom groups were used:

- AARS with psychosis, i.e., aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria *plus* psychosis (hallucinations, delusions)
- AARS without psychosis, i.e., aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria *without* psychosis (hallucinations, delusions)
- Other behavioral symptoms (non-AARS), i.e., hallucinations, delusions, wandering, anxiety, aberrant motor behavior, social interaction problems, depression/dysphoria, apathy/indifference, sleep and night-time behavior disorders, appetite and eating disorders; but not experiencing any AARS symptoms: aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria

Patients with no behavioral symptoms, i.e., patients with CI but without AARS or any other behavioral symptoms, were considered the control group.

The primary outcomes of interest were: HCRU, patient QoL, and caregiver burden. HCRU was measured by number of hospitalizations and consultations in the previous 12 months, and current treatments. Patient QoL was measured by the EuroQol five-dimensional three-level (EQ-5D-3L) instrument, the EuroQol Visual Analogue Scale (EQ-VAS), and the Activities of Daily Living (ADL) questionnaire [18, 19]. The EQ-5D-3L is a descriptive system comprising five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three levels indicating a health state (i.e., no problems, some problems, or extreme problems). Responses were made by ticking the box next to the most appropriate statement in each of the five dimensions; the responses were combined into a five-digit number that described overall health state. The EQ-VAS is a quantitative measure which records health status on a 20 cm vertical VAS on which the endpoints are labelled 100 'Best imaginable health state' to 0 'Worst imaginable health state'. The ADL questionnaire includes 28 items covering basic and instrumental activities organized into six subscales (self-care, household care, employment and recreation, shopping and money, travel, and communication); competence in each area was rated according to a set of four descriptions with scores ranging from 0 to 3, where higher scores indicate greater impairment. Scores from individual items were summed to form subscale scores and then transformed into percentages. Caregiver burden was measured by the EQ-5D-3L, EQ-VAS, the Work Productivity and Activity Impairment (WPAI) questionnaire, and the Zarit Burden Interview (ZBI) [18, 20, 21]. The WPAI questionnaire is a quantitative assessment of the amount of absenteeism, presenteeism, work productivity loss, and activity impairment attributable to a specific health problem, and was measured using six questions and scored using impairment percentages, with higher numbers indicating greater impairment and less productivity. The ZBI is a caregiver self-report measure with 22 items rated on a five-point Likert scale ranging from 0 (never) to 4 (nearly always); the sum of scores ranged between 0 and 88 with higher scores indicating greater burden.

Owing to the potential unreliability of patient responses, the patient QoL measures were completed by the caregiver on patient's behalf and the ADLs

were reported by the physician on the patient record form.

The regression analysis covariates were as follows: categorical AARS variable (AARS with the presence of psychosis, AARS without the presence of psychosis, other behavioral symptoms [non-AARS], no behavioral symptoms), region (Europe versus the US), living situation (nursing home versus community), type of dementia (AD versus other dementias), dementia severity (mild versus moderate versus severe, based on physician's perception of severity), prescriber specialty (specialist physician versus PCP), use of antipsychotics (none versus any), and patient demographics (age, sex, Charlson Comorbidity Index [CCI]). The regression analysis covariates were chosen with the aim of minimizing confounding and were selected based on background knowledge, and included potential confounders commonly seen in dementia studies, such as background characteristics and functional status [13].

Three regression models were used according to the nature of the outcome variable:

- Logistic regression, where the outcome variable was dichotomous
- Negative binomial regression, where the outcome variable was a non-negative count
- Linear regression, where the outcome variable was numeric and was not a non-negative count

Standard errors in regressions were adjusted to allow for intragroup correlation within reporting physician, relaxing the usual requirement that the observations be independent. All analyses were conducted in Stata statistical software Version 16.1 [22].

Ethics

Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such it does not require ethics committee approval or participant consent. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 and Health Information Technology for Economic and Clinical Health Act legislation.

RESULTS

Study population

Record forms were completed by 699 physicians (300 PCPs [42.9%], 58 geriatricians [8.3%], 230 neurologists [32.9%], 47 psychogeriatricians/old age psychiatrists [6.7%], 57 psychiatrists [8.2%], and 7 neuropsychiatrists [1.0%]), providing data for 5,861 patients. The study also included data from 1,357 caregivers.

Table 1 shows the descriptive characteristics of the study sample. The patients' mean age was 76.7 years (median, 78.0 years; range, 38.0–90.0 years), and there was almost an equal number of males and females (53.7% females). The majority of patients had mild dementia (50.8%), followed by moderate (34.6%) and severe (14.6%) disease. Furthermore, just over half of the sample (52.7%) were patients diagnosed as not having an AD type of dementia. With regards to the presence of neurobehavioral symptoms, 646 patients were classified as having AARS with psychosis, 1,884 with AARS without psychosis, 2,245 had other behavioral symptoms (non-AARS), and 1,086 had no behavioral symptoms (controls).

Healthcare resource use

In the overall population, the association between symptom groups and HCRU was confirmed for specific elements of HCRU by regression analysis (see Table 2). Each symptom group had a positive association with HCRU, i.e., HCRU was greater.

Hospitalizations

Statistically significant differences in the number of hospitalizations in the last 12 months, for any condition, were seen in patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with patients with no behavioral symptoms (all $p < 0.001$; Table 2). For hospitalizations in the last 12 months relating to CI, a statistically significant difference was seen only between patients with AARS with psychosis and patients with other behavioral symptoms (non-AARS) (i.e., not in the AARS without psychoses group) compared with patients with no behavioral symptoms. The magnitude of effect was larger in patients with AARS with psychosis versus those without psychosis for both hospitalization outcomes.

A larger number of hospitalizations (for any condition and relating to CI) was also significantly related to: increasing CI (moderate and severe versus mild), CCI, and age (for any condition only); US region versus Europe (relating to CI only); and whether the patient was in a nursing home, being treated by a

Table 1
Patient demographic and clinical characteristics

	Overall	AARS with psychosis[a]	AARS without psychosis[b]	Other behavioral symptoms (non-AARS)[c]	No behavioral symptoms[d]
N	5,861	646	1,884	2,245	1,086
Age, y					
Mean (SD)	76.7 (8.7)	79.8 (8.7)	76.6 (8.6)	76.4 (8.6)	75.9 (8.8)
Median	78.0	81.0	78.0	77.0	77.0
Min, max	38.0, 90.0	51.0, 90.0	43.0, 90.0	38.0, 90.0	39.0, 90.0
Sex, *n* (%)					
Female	3,150 (53.7)	376 (58.2)	943 (50.1)	1,273 (56.7)	558 (51.4)
Dementia severity, *n* (%)					
Mild	2,976 (50.8)	88 (13.6)	808 (42.9)	1,275 (56.8)	805 (74.1)
Moderate	2,027 (34.6)	268 (41.5)	773 (41.0)	749 (33.4)	237 (21.8)
Severe	858 (14.6)	290 (44.9)	303 (16.1)	221 (9.8)	44 (4.1)
CCI					
Mean (SD)	2.6 (1.3)	2.8 (1.6)	2.6 (1.3)	2.5 (1.2)	2.4 (1.1)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	2.0, 12.0	2.0, 12.0	2.0, 12.0	2.0, 11.0	2.0, 10.0
Region, *n* (%)					
Europe	4,651 (79.4)	565 (87.5)	1,486 (78.9)	1,782 (79.4)	818 (75.3)
US	1,210 (20.6)	81 (12.5)	398 (21.1)	463 (20.6)	268 (24.7)
Living situation, *n* (%)					
Not nursing home	5,289 (90.2)	497 (76.9)	1,678 (89.1)	2,081 (92.7)	1,033 (95.1)
Nursing home	572 (9.8)	149 (23.1)	206 (10.9)	164 (7.3)	53 (4.9)
Dementia type, *n* (%)					
Not AD	3,087 (52.7)	245 (37.9)	950 (50.4)	1,194 (53.2)	698 (64.3)
AD	2,774 (47.3)	401 (62.1)	934 (49.6)	1,051 (46.8)	388 (35.7)
Physician specialty, *n* (%)					
PCP	2,452 (41.8)	311 (48.1)	760 (40.3)	932 (41.5)	449 (41.3)
Geriatrician/neurologist	2,447 (41.8)	240 (37.2)	767 (40.7)	931 (41.5)	509 (46.9)
Psychiatrist	962 (16.4)	95 (14.7)	357 (18.9)	382 (17.0)	128 (11.8)
Current antipsychotic use, *n* (%)					
No antipsychotics	5,440 (92.8)	478 (74.0)	1,716 (91.1)	2,167 (96.5)	1,079 (99.4)
Antipsychotics	421 (7.2)	168 (26.0)	168 (8.9)	78 (3.5)	7 (0.6)

[a]AARS with psychosis (aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria plus psychosis [hallucinations, delusions]); [b]AARS without psychosis (aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria without psychosis); [c]Other behavioral symptoms (non-AARS: hallucinations, delusions, wandering, anxiety, aberrant motor behavior, social interaction problems, depression/dysphoria, apathy/indifference, sleep and night-time behavior disorders, appetite and eating disorders; but not experiencing any AARS symptoms: aggression, disinhibition/impulsivity, agitation, irritability/lability, elation/euphoria); [d]No behavioral symptoms (the control group). AARS, agitation/aggression and related symptoms; AD, Alzheimer's disease; CCI, Charlson Comorbidity Index; N/n, number; PCP, primary care physician; SD, standard deviation; US, United States.

specialist physician (geriatrician/neurologist or psychiatrist) versus a PCP, and receiving antipsychotic medication (Supplementary Table 1).

Consultations

Statistically significant differences in the total number of consultations in the last 12 months were seen in patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with patients with no behavioral symptoms (all $p < 0.001$; Table 2). The magnitude of effect was in relatively close range in patients with AARS with psychosis and those with AARS without psychosis. A larger number of consultations was also significantly related to: increasing CI and CCI, US region versus Europe, and whether the patient was being treated by a geriatrician/neurologist versus a PCP (Supplementary Table 1).

Treatments

Statistically significant differences in the current use of any medications and antipsychotic medications were seen in patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with patients with no behavioral symptoms (all $p < 0.001$; Table 2). The magnitude of effect was larger in patients with AARS with versus without psychosis for the use of

Table 2
Regression analysis of HCRU data

	Hospitalizations in the last 12 months (for any condition)			Hospitalizations in the last 12 months (relating to cognitive impairment)			Total consultations in the last 12 months		
	IRR	95% CI	*p*	IRR	95% CI	*p*	IRR	95% CI	*p*
AARS with psychosis	2.20	1.63, 2.97	<0.001	2.00	1.05, 3.81	0.035	1.65	1.32, 2.06	<0.001
AARS without psychosis	1.65	1.25, 2.17	<0.001	1.33	0.72, 2.43	0.361	1.36	1.22, 1.52	<0.001
Other behavioral symptoms (non-AARS)	1.75	1.33, 2.29	<0.001	2.17	1.23, 3.84	0.007	1.20	1.10, 1.31	<0.001
No behavioral symptoms (control)	1			1			1		
	Any current treatment			Current antipsychotic treatment					
	OR	95% CI	*p*	OR	95% CI	*p*			
AARS with psychosis	0.40	0.28, 0.56	<0.001	29.70	13.43, 65.66	<0.001			
AARS without psychosis	0.46	0.38, 0.57	<0.001	10.39	4.76, 22.64	<0.001			
Other behavioral symptoms (non-AARS)	0.61	0.50, 0.74	<0.001	4.51	2.07, 9.82	<0.001			
No behavioral symptoms (control)	1			1					

AARS, agitation/aggression and related symptoms; CI, confidence interval; HCRU, healthcare resource use; IRR, incidence rate ratio; OR, odds ratio.

antipsychotic medication but comparable for the use of any medication.

The use of any medication was also significantly related to: moderate versus mild CI, increasing CCI, US region versus Europe, and whether the patient was in a nursing home, had AD versus non-AD, and was receiving antipsychotic medication (Supplementary Table 1). The use of antipsychotic medication was significantly related to: increasing CI and whether the patient was being treated by a specialist physician (geriatrician/neurologist or psychiatrist) versus a PCP (Supplementary Table 1).

Patient quality of life

In the overall population, the association between symptom groups and measures of patient QoL was confirmed by regression analysis (see Table 3).

EuroQol measures (completed by caregivers on patients' behalf)

Each symptom group had a negative association with both of the proxy EuroQol measures (EQ-5D-3L and EQ-VAS), i.e., patient QoL was decreased.

Statistically significant differences in the EQ-5D-3L and EQ-VAS were seen in patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with patients with no behavioral symptoms (all $p \leq 0.01$; Table 3). The magnitude of effect was comparable in patients with AARS with and without psychosis for the EQ-5D-3L but larger in patients with AARS with psychosis compared with those without psychosis for the EQ-VAS. A decrease in patient QoL was also significantly related to: increasing CI and age, female sex (EQ-5D-3L only), Europe region versus the US, and whether the patient was in a nursing home and being treated by a PCP versus a geriatrician/neurologist (both EQ-5D-3L only) (Supplementary Table 2).

Activities of Daily Living (reported by physicians on patient record forms)

Each symptom group had a positive association with each of the ADL outcomes, i.e., indicating that the patient required more help with the following activities: getting in and out of bed, preparing meals/cooking food, eating, going to the toilet, getting dressed, washing/grooming, walking, travelling out of home, taking medications when required, and the number of ADLs.

Statistically significant differences were seen in patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with those with no behavioral symptoms for all of the ADLs ($p \leq 0.05$) except walking in patients with AARS without psychosis and in patients with other behavioral symptoms (non-AARS) (Table 3). The magnitude of effect was larger in patients with AARS with versus without psychosis for all of the ADL outcomes. Greater need for help with ADLs was also significantly related to several other covariates, including increasing CI and age, and

Table 3
Regression analysis of patient QoL data*

	EQ-5D-3L utility index			EQ-VAS			ADL – Getting in and out of bed		
	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*	OR	95% CI	*p*
AARS with psychosis	–0.23	–0.31, –0.15	<0.001	–8.90	–13.54, –4.27	<0.001	3.17	2.21, 4.54	<0.001
AARS without psychosis	–0.11	–0.15, –0.06	<0.001	–4.41	–7.75, –1.08	0.010	1.61	1.16, 2.23	0.004
Other behavioral symptoms (non-AARS)	–0.08	–0.12, –0.04	<0.001	–4.28	–7.36, –1.19	0.007	1.42	1.05, 1.92	0.024
No behavioral symptoms (control)	0			0			1		
	ADL – Preparing meals/cooking food			ADL – Eating			ADL – Going to the toilet		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
AARS with psychosis	2.20	1.61, 3.01	<0.001	3.52	2.28, 5.43	<0.001	3.79	2.62, 5.48	<0.001
AARS without psychosis	1.86	1.52, 2.29	<0.001	2.03	1.39, 2.95	<0.001	2.25	1.66, 3.05	<0.001
Other behavioral symptoms (non-AARS)	1.60	1.32, 1.94	<0.001	1.46	1.00, 2.13	0.050	1.46	1.08, 1.97	0.014
No behavioral symptoms (control)	1			1			1		
	ADL – Getting dressed			ADL – Washing/grooming			ADL – Walking		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
AARS with psychosis	3.40	2.44, 4.74	<0.001	3.71	2.63, 5.24	<0.001	2.45	1.66, 3.62	<0.001
AARS without psychosis	2.25	1.74, 2.91	<0.001	2.30	1.79, 2.95	<0.001	1.34	0.95, 1.89	0.099
Other behavioral symptoms (non-AARS)	1.68	1.31, 2.16	<0.001	1.91	1.49, 2.44	<0.001	1.08	0.78, 1.52	0.636
No behavioral symptoms (control)	1			1			1		
	ADL – Travelling out of home			ADL – Taking medication when required			Number of ADLs		
	OR	95% CI	*p*	OR	95% CI	*p*	IRR	95% CI	*p*
AARS with psychosis	2.43	1.20, 4.92	0.013	2.41	1.73, 3.34	<0.001	1.30	1.24, 1.36	<0.001
AARS without psychosis	1.70	1.15, 2.52	0.008	1.68	1.38, 2.04	<0.001	1.18	1.13, 1.23	<0.001
Other behavioral symptoms (non-AARS)	1.46	1.02, 2.09	0.040	1.43	1.19, 1.72	<0.001	1.12	1.08, 1.16	<0.001
No behavioral symptoms (control)	1			1			1		

*Proxy EQ-5D-3L and EQ-VAS completed by caregivers on patients' behalf. ADLs were reported by physicians on patient record forms. ADL, Activities of Daily Living; AARS, agitation/aggression and related symptoms; CI, confidence interval; EQ-5D-3L, EuroQol five-dimensional three-level; EQ-VAS, EuroQol Visual Analogue Scale; IRR, incidence rate ratio; OR, odds ratio; QoL, quality of life.

whether the patient was in a nursing home and had a diagnosis of AD, as shown in Supplementary Table 2.

Caregiver burden

In the overall population, the association between symptom groups and measures of caregiver burden was confirmed by regression analysis (see Table 4). In general, patient symptoms were associated with greater caregiver burden.

EuroQol measures

Statistically significant differences in the EQ-5D-3L were seen in caregivers of patients with AARS with psychosis and AARS without psychosis compared with caregivers of patients with no behavioral symptoms (both $p < 0.05$; Table 4). For the EQ-VAS, a statistically significant difference was seen only between caregivers of patients with AARS with psychoses versus caregivers of patients with no behavioral symptoms. The magnitude of effect was identical in caregivers of patients with AARS with and without psychosis using the EQ-5D-3L but slightly larger in caregivers of patients with AARS with psychosis compared with caregivers of patients with AARS without psychosis using the EQ-VAS. A decrease in caregiver QoL was also significantly related to: moderate versus mild CI, severe versus mild CI (EQ-VAS only), increasing patient age (EQ-5D-3L only), Europe region versus the US, and if the patient was not in a nursing home versus in a nursing home (Supplementary Table 3).

Table 4
Regression analysis of caregiver burden data

	EQ-5D-3L utility index			EQ-VAS			WPAI – % impairment while working due to problem		
	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*
AARS with psychosis	–0.05	–0.09, –0.004	0.034	–5.51	–9.76, –1.26	0.011	19.17	9.10, 29.23	<0.001
AARS without psychosis	–0.05	–0.08, –0.02	0.002	–2.20	–5.28, 0.88	0.160	11.12	4.17, 18.06	0.002
Other behavioral symptoms (non-AARS)	–0.03	–0.06, 0.002	0.070	–0.51	–3.55, 2.54	0.745	8.03	1.19, 14.88	0.022
No behavioral symptoms (control)	0			0			0		
	WPAI – % overall work impairment due to problem			WPAI – % activity impairment due to problem			Overall ZBI score		
	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*	Coefficient	95% CI	*p*
AARS with psychosis	20.20	9.34, 31.06	<0.001	9.12	3.18, 15.07	0.003	13.23	9.02, 17.44	<0.001
AARS without psychosis	10.74	3.03, 18.45	0.007	6.51	2.03, 10.98	0.004	9.04	6.13, 11.95	<0.001
Other behavioral symptoms (non-AARS)	8.61	1.25, 15.96	0.022	3.16	–1.13, 7.46	0.148	6.27	3.34, 9.19	<0.001
No behavioral symptoms (control)	0			0			0		

AARS, agitation/aggression and related symptoms; CI, confidence interval; EQ-5D-3L, EuroQol five-dimensional three-level; EQ-VAS, EuroQol Visual Analogue Scale; WPAI, Work Productivity and Activity Impairment; ZBI, Zarit Burden Interview.

Work productivity and activity impairment

Statistically significant differences in the percentage impairment while working, the percentage overall work impairment, and the percentage activity impairment (due to the problem), as measured by the WPAI, were seen in caregivers of patients with AARS with psychosis and AARS without psychosis compared with caregivers of patients with no behavioral symptoms (all $p < 0.01$; Table 4). The difference was significant in caregivers of patients with other behavioral symptoms (non-AARS) versus no behavioral symptoms for the impairment while working and overall work impairment but not for activity impairment. The magnitude of effect was larger in caregivers of patients with AARS with versus without psychosis for all outcomes. Greater caregiver burden related to the WPAI was also significantly related to: moderate versus mild CI, severe versus mild CI (activity impairment only), decreased CCI (overall work impairment only), the patient not being in a nursing home versus being in one, and antipsychotic medication use (activity impairment only) (Supplementary Table 3).

Zarit Burden Interview

Statistically significant differences in the overall ZBI score were seen in caregivers of patients with AARS with psychosis, AARS without psychosis, and with other behavioral symptoms (non-AARS) compared with caregivers of patients with no behavioral symptoms (all $p < 0.001$; Table 4). The magnitude of effect was larger in caregivers of patients with AARS with versus without psychosis. Greater caregiver burden was also significantly related to: increasing CI (moderate and severe versus mild) and the patient not being in a nursing home versus being in one (Supplementary Table 3).

DISCUSSION

We analyzed real-world data for patients with dementia, obtained via their treating physicians and their caregivers. Associations between groups of neurobehavioral symptoms and HCRU, patient QoL, and caregiver burden were examined by multiple regression analyses.

Each symptom group of interest (AARS with psychosis, AARS without psychosis, and other behavioral symptoms [non-AARS]) had a positive association with the HCRU variables of interest (hospitalizations, consultations, and use of medications), i.e., HCRU was greater with the presence of these symptoms. Overall, AARS with psychosis generally had the strongest detrimental effect on the HCRU outcomes: hospitalizations in the last 12 months (for any condition and relating to CI), consultations in the last 12 months, and current antipsychotic treatment, compared with patients with AARS without psychosis and patients with no behavioral symptoms (the control group).

In addition, each symptom group had a negative association with proxy measures of patient QoL (the EQ-5D-3L and EQ-VAS), i.e., patient QoL was decreased. The magnitude of effect was comparable in patients with AARS with and without psychosis for the EQ-5D-3L measure but larger in patients with AARS with psychosis compared with those with AARS without psychosis for the EQ-VAS. Furthermore, each symptom group had a positive association with each ADL outcome, indicating that patients with these symptoms required greater help with everyday activities. The magnitude of effect was clearly largest in patients with AARS with psychosis versus the other symptom groups, i.e., they required the greatest help with ADLs.

In general, symptom groups were also associated with greater caregiver burden as seen through measures of caregiver QoL (EQ-5D-3L and EQ-VAS), effects on work and activity impairment (WPAI), and the impact of patient dementia on their life (ZBI). As with the other measures, the magnitude of the effect was generally larger in caregivers of patients with AARS with psychosis versus caregivers of patients with AARS without psychosis.

Regression analysis covariates that were found to be most often significantly related to the outcomes were dementia severity (moderate and severe versus mild) and patients' living situation (whether they were in nursing home versus in the community). Of interest, several covariates differed between locations in Europe compared with in the US; for example, a larger number of hospitalizations for CI, total consultations, and the use of any treatment were seen in the US versus Europe. Whereas a decrease in patient and caregiver QoL was significantly related to the Europe region versus the US. This warrants further investigation but could potentially be owing to the different healthcare and funding environments between Europe and the US; for example, there are more government owned and run universal healthcare systems in Europe compared with American hybrid (predominantly private sector) systems and generally higher healthcare spending.

Overall, all three symptom groups had detrimental effects on HCRU, patient QoL, and caregiver burden, which highlights the overall burden of CI/dementia. To add to this, the higher the neurobehavioral symptom burden, particularly aggressive, agitated symptoms with additional psychosis, the more detrimental effect it seemed to have on health-related outcomes. The finding that patients' dementia severity and living situation were the factors most related to the outcomes is not surprising. It makes sense that increasing disease severity increases burden, owing to patients' increasing needs as their disease progresses, and several studies support this finding [6, 14, 15]. Still, this relationship is not clear cut as there are a number of other studies which have found that neurobehavioral symptoms are relatively stable across CI and dementia stages [4, 11–13]. A community versus a nursing home living situation was particularly detrimental to caregiver burden. This could also be expected as community living would put increased pressure on caregivers, owing to the lack of formal or additional care associated with living at home.

Our results are also in agreement with previous research showing that AARS and psychosis are consistent problems for caregivers across the whole range of dementias [4]. For example, aggression and agitation are some of the most frequently cited symptoms associated with caregiver depression, burden, and burnout [6, 10, 23, 24]. Plus, neurobehavioral symptoms are often cited as one of the main reasons for referring patients to nursing homes, and in particular symptoms such as physical aggression, psychosis, anxiety, hallucinations, and depression [25].

Detrimental effects of dementia on patient QoL, HCRU, and costs have also been previously reported. For example, Handels et al. (2018) reported costs related to formal and informal care use, and patient-reported and proxy QoL in patients with dementia in 8 European countries, noticing differences due to organization and management of care between countries [26]. We believe the current study is the first of its kind, adding evidence of the specific burden of neurobehavioral symptoms to previously described factors contributing to lower patient QoL, greater HCRU, and caregiver burden.

According to a consensus statement by Finkel et al. (1996), 'The behavioral and neuropsychological signs and symptoms of dementia are integral elements of the disease process and, therefore, are a legitimate concern of healthcare providers. These symptoms present severe problems to all those who interact with the patients as well as to the patients themselves, and to society and its health services' [9]. In a consensus paper from the EADC, Robert et al. (2005) suggested that further understanding of these symptoms was needed as it may offer better treatment opportunities [2]. The current results are in agreement with previous findings that have suggested the presence of groups of symptoms in dementia that can be studied together, which might strengthen results, expose differences in their etiology, and lead to new options for

treatment [4]. However, at this stage in the research there is a large amount of individual variability, and distinct symptom groups have yet to be established.

The current study offers a number of applications and implications for ongoing research. For example, there are implications for intervention development, and identifying patients and caregivers at risk of problems, e.g., depression and burnout. The research suggests that particular support should be given to caregivers of patients expressing aggression, agitation, and other neurobehavioral symptoms [24].

Furthermore, while there are currently no effective treatments to slow the progression of CI in dementia, there are a range of interventions that may help to manage neurobehavioral symptoms. Although treating AARS in dementia is seen as a major challenge, practical strategies can be applied for common behavioral symptoms, including using both non-pharmacologic measures (such as ergotherapy, physical therapy, music therapy, and work with family members) and medications (e.g., risperidone, haloperidol, or aripiprazole for agitation and aggressiveness) [27, 28].

Future research should focus on building a consensus on how to study AARS symptoms, e.g., whether they should be treated as single symptoms or in clusters, taking into account correlations with other similar symptoms. van der Linde et al. (2013) highlighted the issue of heterogeneity of symptoms in their literature review and suggested that authors should carefully address their research questions and hypotheses to decide if symptoms should be studied in groups or individually [4]. Finkel et al. (1996) offered their views on the importance of developing more applicable methods for assessing neurobehavioral signs and symptoms, including longitudinal evaluations; and of further work on their underlying pathogenic mechanisms and the clinical, social, and societal impact [9]. Finally, aging populations and demographic changes suggest that countries around the world are facing huge challenges in the current and future long-term management and funding of people with dementia [26].

This study has several limitations that should be considered. For example, the sample collected was pseudo-random rather than a truly random sample, since the physicians were required to collect data for the next 10 consecutively consulting patients. The retrospective nature of the data collection meant that the methodology relied on accurate reporting by physicians and caregivers. In light of this, missing data were to be expected and may have influenced results, and there may have been recall bias. Missing data can cause various problems, such as reducing statistical power and precision, causing bias, and reducing the representativeness of the sample, which may affect the conclusions that can be drawn from the data. In light of this, the missing values for each variable of interest are presented in Supplementary Table 4 and should be considered when interpreting the results.

Owing to the potential unreliability of self-reported patient responses, particularly from those with more severe levels of CI, the patient QoL measures were completed by the caregiver on the patients' behalf and the ADLs were reported by the physician on the patient record form. However, this approach could have led to inaccuracies, as demonstrated in some other studies which have shown a degree of discordance between patient- and caregiver-reported QoL; particularly with caregivers reporting lower levels of patient QoL compared with patient self-evaluations [29–31]. Also, it is uncertain how frequently physicians would have directly observed ADLs.

Furthermore, this was a point-in-time rather than a longitudinal survey, which meant data may have been used to assess the association between factors but not causality. Another potential limitation was that only 53.7% of patients were female, whereas a predominance of female dementia patients has generally been reported [32, 33]. There was also low number of patients with severe CI; the patient population was heavily weighted towards those with mild to moderate disease. Likewise, there were other features of the sample that merit further discussion. For example, there was low current use of antipsychotic medication (in 7.2% of patients), which could be associated with the small number of psychiatrists in the physician population (16.4% versus 41.8% for both PCPs and geriatricians/neurologists). In addition, a much higher proportion of patients were living at home compared with in a nursing home (90.2% versus 9.8%), which could be linked to the generally mild to moderate versus severe dementia population. There was also a smaller number of responses from caregivers compared with patients: 1,357 and 5,861 respondents, respectively. This could be because participation in the survey was voluntary or perhaps owing to an element of bias, where caregivers of more severe patients were more likely to have responded.

In line with previous findings, the majority (> 80%) of dementia patients in this study experienced neurobehavioral symptoms. However, although most of the patients without behavioral symptoms (a total of 1,086 patients) had mild dementia (74.1%),

compared with 21.8% with moderate and 4.1% with severe dementia, previous research has suggested that several neurobehavioral symptoms, including depression, irritability, and night-time disturbances, could be present at prodromal or early stages in various dementias [6, 11]. This did not seem to be evident in our study population and may suggest an element of bias as very severe patients may not have consulted as often.

This study also has a number of strengths. For example, it included a large sample size from multiple study sites and countries. The setting was reflective of real-world practice, which is important for future decision-making regarding forthcoming clinical studies, new treatment options, and research and development. The study also used a wide variety of instruments to measure HCRU, proxy patient QoL, and caregiver burden. Some of the included instruments have been specially designed, for example, to reflect the stresses of caregivers of dementia patients (e.g., the ZBI).

In conclusion, this study suggests that certain combinations of behaviors, involving AARS and psychosis, may impact health-related outcomes such as HCRU, patient QoL, and caregiver burden in dementia. Our results have implications for intervention development for dementia patients who report clusters of symptoms and their caregivers, and for identifying patients or caregivers at risk of problems.

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SUPPLEMENTARY MATERIAL

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