A real-world assessment of healthcare costs associated with agitation in Alzheimer's dementia

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BACKGROUND

- Neuropsychiatric symptoms, such as agitation, may negatively impact cognitive performance and patient and caregiver quality of life in individuals living with Alzheimer's dementia (AD)[1,2]
- There is little information on healthcare costs associated with agitation associated with AD (AAD) as until recently, there were no International Classification of Diseases, Tenth revision, Clinical Modification [ICD-10-CM] diagnosis codes specific to this symptom allowed for identification in claims databases

OBJECTIVE

To assess the incremental economic burden of agitation in patients with AD in the United States, by combining administrative claims data with electronic medical records (EMR)

METHODS

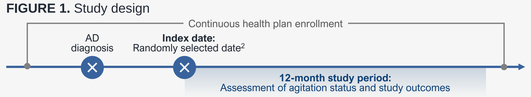
Data Source

- This study used the Reliant Medical Group Database (January 1, 2016 - March 31, 2020), an integrated delivery network in Massachusetts that covers over 1.2 million lives annually
  - Data included a combination of administrative health insurance claims data, EMR, and patient-level information from medical chart abstraction using an electronic case report form (eCRF) designed specifically for this study
  - This allowed for the identification of patients experiencing specific agitation behaviors[3] (i.e., information that is typically not documented in prepopulated EMR data)

Study Design

- A retrospective cohort design was used **(Figure 1)**
- This study received an exemption from the Western Copernicus Group (WCG) Institutional Review Board (IRB)

FIGURE 1. Study design

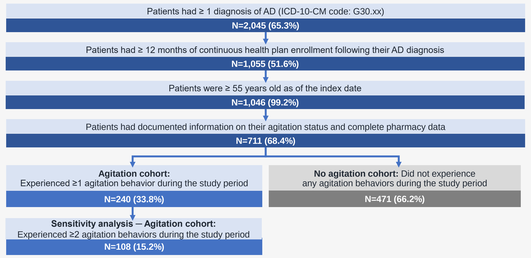


Note: [1]AD diagnoses were identified using International Classification of Diseases, Tenth revision, Clinical Modification [ICD-10-CM] codes G30.xx. [2]A random date after AD diagnosis was selected as the index date to capture a range of disease severity.

Study Population

- Eligible AD patients aged ≥55 years were identified in the administrative claims data and unique coded IDs were used to extract information from their EMR **(Figure 2)**
- Patients were classified into 2 study cohorts based on the presence of agitation:

FIGURE 2. Sample selection flowchart



Measures, Outcomes, and Statistical Analyses

- Patient characteristics, including AD-related clinical characteristics, were descriptively reported for each cohort using means, medians, and standard deviations for continuous variables and frequency counts and percentages for categorical variables
  - Among the *agitation cohort*, agitation behaviors during the study period were reported
- Annual all-cause and AD-related healthcare costs (defined as costs for claims during which a diagnosis for AD was recorded) were reported for the *agitation* and *no agitation cohorts* separately
  - Entropy balancing was used to create cohorts with similar characteristics
  - Healthcare costs were compared across balanced cohorts using weighted regression analyses

RESULTS

Patient Characteristics

- Among 711 patients included in the study, 240 were classified in the *agitation cohort* and 471 in the *no agitation cohort* **(Figure 1)**
- After balancing, patients in both cohorts were aged 85 years old, 66.7% were female, and 42.5% presented with moderate to severe AD **(Table 1)**

TABLE 1. Patient characteristics

	Before weighting			After weighting[1]		
Number of patients, N	Agitation cohort N = 240	No agitation cohort N = 471	Std. diff.	Agitation cohort N = 240	No agitation cohort N = 471	Std. diff.
At the index date						
Age, mean ± SD [median]	84.9 ± 7.7 [86.0]	84.9 ± 7.8 [86.0]	0.00	84.9 ± 7.7 [86.0]	84.8 ± 7.7 [86.0]	0.01
Female gender, n (%)	160 (66.7%)	359 (76.2%)	0.21*	160 (66.7%)	314 (66.7%)	0.00
Race, n (%)						
White	203 (84.6%)	395 (83.9%)	0.02	203 (84.6%)	398 (84.5%)	0.00
African American or Black	1 (0.4%)	6 (1.3%)	0.09	1 (0.4%)	11 (2.3%)	0.16*
Asian	2 (0.8%)	4 (0.8%)	0.00	2 (0.8%)	4 (0.8%)	0.01
Native American or Alaskan Native	3 (1.3%)	2 (0.4%)	0.09	3 (1.3%)	4 (0.8%)	0.04
Unknown	31 (12.9%)	64 (13.6%)	0.02	31 (12.9%)	55 (11.7%)	0.04
Non-Hispanic ethnicity, n (%)	185 (77.1%)	342 (72.6%)	0.10*	185 (77.1%)	363 (77.1%)	0.00
Calendar year, n (%)						
2016	71 (29.6%)	139 (29.5%)	0.00	71 (29.6%)	139 (29.5%)	0.00
2017	58 (24.2%)	126 (26.8%)	0.06	58 (24.2%)	114 (24.2%)	0.00
2018	81 (33.8%)	155 (32.9%)	0.02	81 (33.8%)	159 (33.8%)	0.00
2019	30 (12.5%)	51 (10.8%)	0.05	30 (12.5%)	59 (12.5%)	0.00
Primary residence, n (%)						
Private residence	111 (46.3%)	216 (45.9%)	0.01	111 (46.3%)	218 (46.3%)	0.00
SNF, nursing home, hospital, or hospice	95 (39.6%)	120 (25.5%)	0.31*	95 (39.6%)	186 (39.5%)	0.00
Assisted living, adult family home, or boarding home	23 (9.6%)	62 (13.2%)	0.11*	23 (9.6%)	45 (9.6%)	0.00
Retirement community or independent group living	3 (1.3%)	11 (2.3%)	0.08	3 (1.3%)	6 (1.3%)	0.01
Unknown	8 (3.3%)	62 (13.2%)	0.36*	8 (3.3%)	16 (3.4%)	0.00
Living situation, n (%)						
Lives in a group home	118 (49.2%)	183 (38.9%)	0.21*	118 (49.2%)	231 (49.0%)	0.00
Lives with one other person	74 (30.8%)	146 (31.0%)	0.00	74 (30.8%)	145 (30.8%)	0.00
Lives alone	22 (9.2%)	54 (11.5%)	0.08	22 (9.2%)	43 (9.1%)	0.00
Lives with a group in a private residence	16 (6.7%)	23 (4.9%)	0.08	16 (6.7%)	31 (6.6%)	0.00
Unknown	7 (2.9%)	61 (13.0%)	0.38*	7 (2.9%)	14 (3.0%)	0.00
Smoking history, n (%)						
Current smoker	6 (2.5%)	5 (1.1%)	0.11*	6 (2.5%)	12 (2.5%)	0.00
Former smoker	78 (32.5%)	171 (36.3%)	0.08	78 (32.5%)	153 (32.5%)	0.00
Never smoker	91 (37.9%)	162 (34.4%)	0.07	91 (37.9%)	179 (38.0%)	0.00
Unknown	65 (27.1%)	133 (28.2%)	0.03	65 (27.1%)	127 (27.0%)	0.00
Severity of AD/dementia, n (%)						
Mild	19 (7.9%)	61 (13.0%)	0.17*	19 (7.9%)	37 (7.9%)	0.00
Moderate	23 (9.6%)	53 (11.3%)	0.06	23 (9.6%)	45 (9.6%)	0.00
Severe	79 (32.9%)	88 (18.7%)	0.33*	79 (32.9%)	155 (32.9%)	0.00
Unknown	119 (49.6%)	269 (57.1%)	0.15*	119 (49.6%)	233 (49.5%)	0.00
At any time						
Year of AD/dementia diagnosis, n (%)						
≤ 2015	129 (53.8%)	254 (53.9%)	0.00	129 (53.8%)	265 (56.3%)	0.05
2016	50 (20.8%)	81 (17.2%)	0.09	50 (20.8%)	74 (15.7%)	0.14*
2017	26 (10.8%)	65 (13.8%)	0.09	26 (10.8%)	62 (13.2%)	0.07
2018	24 (10.0%)	49 (10.4%)	0.01	24 (10.0%)	49 (10.4%)	0.02
2019	5 (2.1%)	9 (1.9%)	0.01	5 (2.1%)	9 (1.9%)	0.02
Unknown	6 (2.5%)	13 (2.8%)	0.02	6 (2.5%)	12 (2.5%)	0.00
Time from first onset of AD/dementia symptoms to diagnosis (years)[2], mean ± SD [median]	2.5 ± 2.7 [2.0]	2.0 ± 2.2 [1.5]	0.19*	2.5 ± 2.7 [2.0]	2.3 ± 2.3 [2.0]	0.08
Time from AD/dementia diagnosis to index date (years)[2], mean ± SD [median]	2.8 ± 2.5 [2.0]	2.8 ± 2.8 [2.0]	0.02	2.8 ± 2.5 [2.0]	2.8 ± 2.7 [2.0]	0.02
Time from first onset of AD/dementia symptoms to index date (years)[2], mean ± SD [median]	5.2 ± 3.6 [5.0]	4.5 ± 3.3 [4.0]	0.20*	5.2 ± 3.6 [5.0]	4.8 ± 3.2 [4.0]	0.11*
During the 6-month period prior to the index date						
CCI score, mean ± SD [median]	3.4 ± 1.8 [3.0]	3.2 ± 1.9 [3.0]	0.13*	3.4 ± 1.8 [3.0]	3.4 ± 1.8 [3.0]	0.00

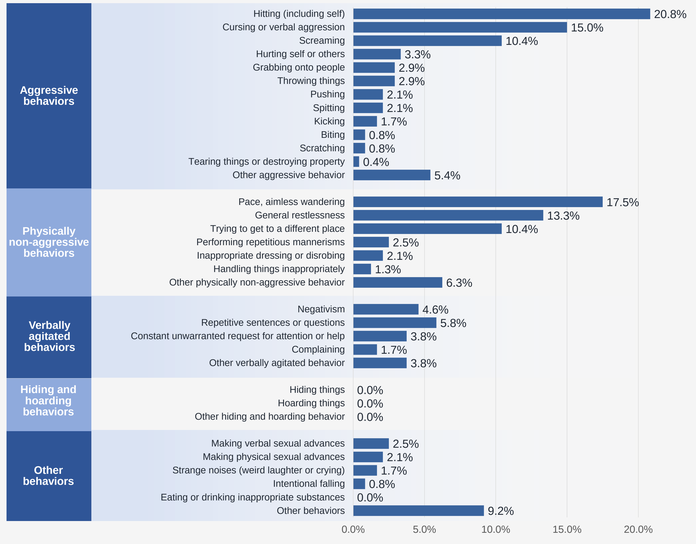
Abbreviations: AD: Alzheimer's dementia; CCI: Charlson Comorbidity Index; N: number; SD: standard deviation; SNF: skilled nursing facility; std. diff: standardized difference

Notes: *Standardized difference > 0.1; [1]Entropy balancing was used to balance key characteristics that may have an impact on the outcomes of interest between the agitation cohort and the no agitation cohort (i.e., age, sex, race, ethnicity, calendar year of index date, smoking history, time from first onset of AD/dementia symptoms to diagnosis, time from AD/dementia diagnosis to index date, time from first onset of AD/dementia symptoms to index date, severity of AD/dementia, primary residence, living situation, and CCI score). Patients in the no agitation cohort were assigned weights such that the distribution of key characteristics had the same mean and standard deviation as the agitation cohort. Subject to rounding exceptions, weights were normalized so that the sum of weights was equal to the number of patients in each cohort; [2]The amount of time was estimated based on years rather than exact dates.

Agitation Characteristics

- On average, patients in the *agitation cohort* 1.9 agitation behaviors recorded in their medical chart during the study period
- The most frequently recorded agitation behaviors were physically and verbally aggressive behaviors (40.4%) and physically non-aggressive behaviors (38.8%)
  - Common aggressive behaviors included hitting (20.8%), cursing or verbal aggression (15.0%), and screaming (10.4%; **Figure 3**)
  - Common physically non-aggressive behaviors included pacing/aimless wandering (17.5%), general restlessness (13.3%), and trying to get to a different place (10.4%; **Figure 3**)

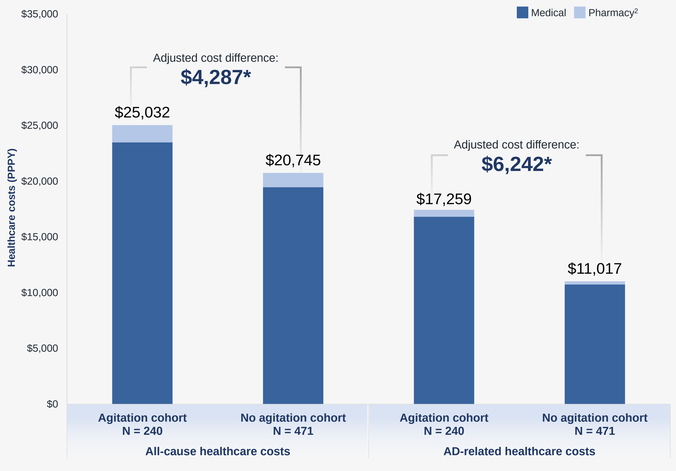
FIGURE 3. Agitation during the study period



Healthcare Costs

- Total adjusted all-cause healthcare costs were $4,287 higher (or 20.7% greater) in the *agitation cohort* versus the *no agitation cohort* ($25,032 vs. $20,745; p=0.04; **Figure 4**)
  - Inpatient hospital costs accounted for $2,151 (or 50.2%) of this cost difference (*agitation* vs. *no agitation cohort*: $4,801 vs. $2,650; p<0.01)
- AD-related costs accounted for the majority of healthcare costs (68.9% in the *agitation cohort* and 53.1% in the *no agitation cohort*)
- Total adjusted AD-related healthcare costs were $6,242 higher (or 56.7% greater) in the *agitation cohort* versus the *no agitation cohort* ($17,259 vs. $11,017; p<0.01; **Figure 4**)

FIGURE 4. Healthcare costs during the study period[1]



Abbreviations: AD: Alzheimer's dementia; PPPY: per-patient-per-year

Note: *Indicates statistical significance at the 5% level; [1]The adjusted cost difference for each outcome was estimated using weighted two-part models, where the first part was a logistic model with a binomial distribution and the second part was a generalized linear regression model with a log link and a gamma distribution. The model used 499 bootstraps and was reweighted 499 times; [2]For AD-related healthcare costs, pharmacy costs represented only those associated with use of antidementia, antidepressant, antipsychotic, and antianxiety medication.

SENSITVITY ANALYSIS

- With a more conservative definition of agitation, 108 patients were classified in the *agitation cohort* and patient characteristics were similar to the main analysis
- Total **all-cause** healthcare costs were $5,559 higher (24.6% greater) in the *agitation cohort* versus the *no agitation cohort* ($27,576 vs. $22,127; p=0.02)
- Similarly, **AD-related** healthcare costs were $8,682 higher (74.8% greater; $20,288 vs. $11,606; p<0.01) in the *agitation cohort*

LIMITATIONS

- Since the study population only included commercially insured patients from an integrated delivery network in Massachusetts, results may not be generalizable to the US population with AD
- Information captured by the study's eCRF was limited to information available in the patients' medical records, thus patients may have been misclassified in the no agitation cohort if agitation behaviors were not systematically recorded
- Accordingly, the frequency of agitation behaviors reported may be influenced by those that are more likely to be documented by physicians (e.g., prominent aggressive behaviors)
- Despite balancing, there may be residual confounding due to unobservable confounders. No causal inference can be made from this retrospective study

CONCLUSION

- Among patients with AD, agitation was associated with increased healthcare costs, highlighting the additional clinical burden that agitation poses on patients
  - Having at least 2 agitation behaviors was associated with an even higher incremental cost of agitation
- Strategies focusing on improving agitation management have the potential to mitigate the burden associated with AD

REFERENCES

1. Phan SV, et al. *Drugs R D.* 2019;19(2):93-115.
2. Carrarini C, et al. *Front Neurol.* 2021;12:644317.
3. Cohen-Mansfield J. Instruction manual for the Cohen-Mansfield Agitation Inventory (CMAI) Rockville, MD: The Research Institute of the Hebrew Home of Greater Washington;1991

DISCLOSURES

This work was supported by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck LLC. GG served as a clinical consultant. JA and JS are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. AU is an employee of Lundbeck LLC. RB, MC, MGL, DC, and AG are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Otsuka Pharmaceutical Development & Commercialization, Inc.

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