

Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia

Rachel Halpern¹ | Jerald Seare¹ | Junliang Tong¹ | Ann Hartry² | Anthony Olaoye³ | Myrlene Sanon Aigbogun⁴

¹Health Economics and Outcomes Research, Optum, Eden Prairie, Minnesota

²Health Economics and Outcomes Research, Lundbeck LLC, Deerfield, Illinois

³Business Analytics, Otsuka America Pharmaceuticals, Princeton, New Jersey

⁴Health Economics and Outcomes Research, Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey

Correspondence

Rachel Halpern, PhD, Health Economics and Outcomes Research, Optum, 11000 Optum Circle, Eden Prairie, MN 55344.
Email: rachel.halpern@optum.com

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Background: Agitation is a common neuropsychiatric symptom of Alzheimer disease (AD). Data are scarce regarding agitation prevalence among community-dwelling patients with AD.

Objective: To estimate agitation prevalence in a sample of US patients with AD/dementia overall and by AD/dementia disease severity, using data from electronic health records (EHR).

Methods: This retrospective database study examined community-dwelling patients with ≥ 1 EHR record indicating AD/dementia from January 2008 to June 2015 and no evidence of non-Alzheimer dementia during the 12-month preindex and postindex periods. Agitation was identified using diagnosis codes for dementia with behavioral disturbance and EHR abstracted notes records indicating agitation symptoms compiled from the International Psychogeriatric Association provisional consensus definition.

Results: Of 320 886 eligible patients (mean age, 76.4 y, 64.7% female), 143 160 (44.6%) had evidence of agitation during the observation period. Less than 5% of patients with agitation had a diagnosis code for behavioral disturbance. The most prevalent symptom categories among patients with agitation, preindex and postindex, were agitation (31.4% and 41.3%), falling (22.6% and 21.7%), and restlessness (18.3% and 23.3%). Among the 78 827 patients (24.6%) with known AD/dementia severity, agitation prevalence was 61.3%. Agitation during the observation period was most prevalent for moderate-to-severe and severe AD/dementia (74.6% and 68.3%, respectively) and lowest for mild AD/dementia (56.4%).

Conclusions: Agitation prevalence was 44.6% overall and 61.3% among patients with staged AD/dementia. Behavioral disturbance appeared to be underdiagnosed. While agitation has previously been shown to be highly prevalent in the long-term care setting, this study indicates that it is also common among community-dwelling patients.

KEYWORDS

agitation, Alzheimer disease, behavioral disturbance, dementia, disease progression, electronic health records, prevalence, retrospective studies

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1 | INTRODUCTION

The global burden of Alzheimer disease (AD) is growing rapidly with the aging of the world's population: There were an estimated 35.6 million people living with dementia worldwide in 2010, with numbers predicted to nearly double every 20 years.¹ In the United States, the number of adults age 65 and older with AD is expected to reach 7.1 million by 2025—a nearly 35% increase from the 5.3 million affected individuals in 2017.²

Patients with AD are affected not only by the memory loss and cognitive decline that are hallmarks of the disease but also by a wide range of neuropsychiatric symptoms (NPS) that include agitation, mood disorders, psychosis, and sleep disturbances.³ NPS are experienced by nearly all patients with dementia at some point during the course of their disease⁴⁻⁶ and exacerbate the already substantial social and economic burden exacted by AD, contributing to increased morbidity, mortality, and institutionalization among patients with AD^{7,8} and to psychological distress and other health problems among their caregivers.^{2,8-10} In fact, the effect of NPS on patient and caregiver quality of life is consistently found to be even more detrimental than that of functional or cognitive impairment,^{7,9,11-13} leading to widespread acknowledgement of NPS as a public health priority in neurodegenerative disease.³

Agitation, characterized by excessive psychomotor activity, physical or verbal aggression, disruptive irritability, and disinhibition,³ is one of the most common NPS among patients with dementia, with prevalence estimates ranging from 40% to 60%.^{4,14-17} In addition to being one of the most distressing NPS for caregivers,^{10,14} agitation has been associated with faster progression to severe dementia, functional decline, increased risk of institutionalization, and earlier death.¹⁸⁻²⁵ Management of agitation is thus a critical factor in the care of patients with AD, but no drugs at present have been approved in the United States for treating agitation in the population with dementia. Clinicians therefore turn to off-label prescription of antipsychotics, sedatives, and other psychoactive drugs when nonpharmacological approaches are insufficient and/or patients' symptoms are severe. Unfortunately, these treatments are limited by concerns regarding efficacy, safety, and tolerability.^{3,26}

Although recent progress in elucidating the mechanisms that may underlie NPS has spurred optimism regarding potential pharmacological treatments for AD, clinical research in the field has historically been hampered by heterogeneity in entry criteria and outcome measures among studies.³ To help advance research into agitation among patients with dementia, the International Psychogeriatric Association (IPA) in 2015 released a provisional consensus definition that broadly defined agitation as excessive motor activity or verbal/physical aggression that (1) occurs in a patient with cognitive impairment or dementia syndrome, (2) is accompanied by evidence of emotional distress, (3) results in disability beyond that caused by cognitive impairment, and (4) is not solely attributable to another condition.²⁷ Development and utilization of this definition are expected to facilitate high-quality clinical and epidemiological investigations addressing agitation among patients with AD and other cognitive disorders by helping to define study populations and standardize baseline assessment.²⁷

Key points

- In this large sample of patients with Alzheimer disease (AD)/dementia, 44.6% of all patients and 61.3% of those whose AD/dementia severity could be determined had electronic health records (EHR) documentation of agitation symptoms over 2 years.
- Less than 5% of patients identified with agitation had a diagnosis code for behavioral disturbance in the EHR diagnosis table. While the EHR diagnosis table does not reflect claims submitted for payment, this finding may suggest that behavioral disturbance is underrepresented in claims data.
- The prevalence of agitation was highest among patients with moderate-to-severe and severe AD/dementia.
- While a majority of published studies have shown a high prevalence of agitation in the long-term care setting, this study indicates that agitation is also common among community-dwelling patients.

Given the profound impact of NPS on quality of life and the evidence that the presence of these symptoms may affect the course of AD, the relationship between agitation and AD disease stage is an important research target that could help inform both study design and treatment decisions.²⁸ However, little has been published on the overall prevalence of agitation among community-based patients, and existing data originate from clinical studies that used specialized rating scales and/or psychiatric evaluations that may not be widely performed in real-world practice.²⁹⁻³¹ We therefore conducted an analysis to estimate the prevalence of agitation symptoms in a sample of US patients with AD/dementia and the prevalence of agitation by AD/dementia disease severity. This study was performed using terms consistent with the IPA provisional definition of agitation in conjunction with data from electronic health records (EHR), which leverages information from patients' medical records to provide a wide range of clinical data on a population level.

2 | MATERIALS AND METHODS

2.1 | Data source

This was a retrospective observational analysis using data from the Optum Clinical Electronic Health Record Database, which contains deidentified and aggregated clinical and medical administrative data from more than 54 US health care delivery organizations, including more than 140 000 providers at more than 700 hospitals and 7000 clinics. These data come from all EHR capture systems submitted by participating organizations. Data are obtained from physician offices, emergency rooms, laboratories, and hospitals and include demographic information, vital signs, and other observable measurements, medications prescribed and administered, laboratory test results,

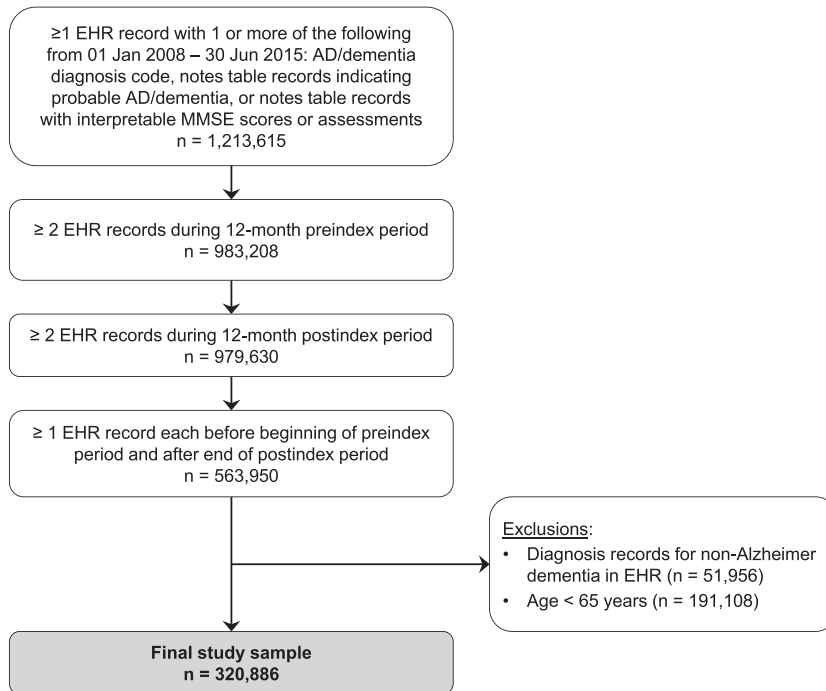


FIGURE 1 Sample selection and attrition flow diagram. AD, Alzheimer disease; EHR, electronic health records; MMSE, Mini-Mental Status Examination

administrative data for clinical and inpatient stays, and coded diagnoses and procedures. At the time of data extraction, the database contained records for approximately 47 million primarily community-dwelling patients across the United States and Puerto Rico, with an average of 45 months of observed data per patient. Because no identifiable protected health information was extracted or accessed during the course of the study, institutional review board approval or waiver of authorization was not required.

In addition to the data described above, the key EHR data for this study comprised abstracted provider notes records, which were extracted from electronic notes via a natural language processing (NLP) system developed and maintained by Optum Analytics (OA; Boston, Massachusetts). The NLP system captures words and phrases from unstructured text in clinical notes—including conditions, signs and symptoms, family history, disease-related scores and diagnostic procedures, medication changes, and physician rationale for prescribing decisions—and converts them into abstracted notes records that contain deidentified, consistently formatted content for analysis. The abstracted notes records output via NLP consist of the main terms, such as conditions (eg, Alzheimer disease) or symptoms (eg, agitation), accompanied by additional data fields that provide context; these supporting fields contain terms relating to severity/frequency/duration, body part or measurement value, medical chart section, and qualifiers such as negation or progress in the diagnostic process or input from family members. Main terms of interest for the NLP system were identified using vocabulary from the Unified Medical Language System, which includes medical dictionaries such as the Logical Observation Identifiers Names and Codes, the Systemized Nomenclature of Medicine-Clinical Terms, and RxNorm (a listing of generic and branded drugs), among others. New NLP concepts are created, and the performance of the NLP system is verified, by a team of medical terminologists and clinicians from OA that assesses the accuracy of the NLP output compared with a manual review of sample EHR notes.

For this study, abstracted notes records to identify AD/dementia and agitation were reviewed manually by Optum's medical director to determine whether the overall combinations of terms in the notes record fields were indicative of probable AD/dementia and agitation (eg, pertained to patient behavior or disposition and were not negation).

2.2 | Study sample selection

The initial sample (Figure 1) comprised patients aged 65 years and older who had at least one EHR record with one or more of the following during the period of January 2008 through June 2015 (patient identification period): (1) at least one International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code for AD/dementia (Table A1); (2) abstracted notes records from direct physician encounters that indicated "probable" AD/dementia*; or (3) notes records with interpretable Mini-Mental Status Examination (MMSE) scores or assessments. In all, 550 394 different term combinations representing a total of 13 139 781 abstracted notes records were reviewed to identify patients with probable AD/dementia. Index dates were defined hierarchically, as follows. For patients who had an explicit AD/dementia severity level (ie, at least one notes record for probable AD/dementia with an explicit severity level and/or at least one notes record with a valid MMSE

*"Probable" for this analysis meant it was inferred that the patient had the condition or symptom of interest based on clinician review of the terms in the abstracted provider notes records. Notes records that indicated patients did not have dementia, did not indicate direct observation of the patient and his or her symptoms, contained uninterpretable or invalid MMSE scores, or were not from direct physician encounters were not categorized as "probable." Main terms for AD/dementia were Alzheimer disease, Alzheimer dementia, dementia, senile dementia, presenile dementia, multiple infarction dementia, vascular dementia, subcortical vascular dementia, and arteriosclerotic dementia.

score indicating mild, moderate, or severe AD/dementia), the index date was the date of the first record with an explicit severity level. For patients with at least one notes record indicating probable AD/dementia but no records indicating explicit severity, the index date was the date of the first record indicating probable AD/dementia. Finally, for patients who had no notes records indicating probable AD/dementia, the index date was the date of the first AD/dementia diagnosis record. To be included in the final study sample, patients were required to have at least two EHR records each during the 12 months before and after the index date (preindex and postindex periods, respectively), at least one EHR record each before the beginning of the preindex period and after the end of the postindex period, and no EHR diagnosis records for non-Alzheimer dementia during the preindex or postindex periods (Table A2).

2.3 | Study measures

Preindex patient characteristics included age, sex, and Charlson comorbidity score,³² which was calculated using EHR diagnosis records during the preindex period. Patients with agitation during the preindex and postindex periods were identified on the basis of diagnosis table records with diagnosis codes for dementia with behavioral disturbance (ICD-9-CM 294.11, 294.21; ICD-10-CM F01.51, F02.81, F03.91) and information extracted from EHR notes. To identify agitation from EHR notes, agitation-related symptoms were compiled from the 2015 IPA consensus definition²⁷ (Table 1) and abstracted notes records with agitation-related main terms were reviewed to identify those indicating probable agitation symptoms. The final list included 126 main terms from notes records, categorized into 19 symptoms (Table A3). In all, 1 396 455 different term combinations representing a total of 44 539 115 abstracted notes records were manually reviewed to identify probable agitation. Patients with agitation symptoms were identified with a binary indicator.

2.4 | AD/dementia severity categorization

AD/dementia severity category assignments were based on MMSE scores and physician notes (Table 2). Patients who had notes records containing valid quantitative MMSE scores or explicit terms for only one level of AD/dementia severity during the postindex period were categorized accordingly as "mild," "mild-to-moderate," "moderate," "moderate-to-severe," or "severe." For patients whose notes records contained multiple severity levels, a severity category was determined by examining the chronological distribution of severity levels, as described in Table 2. Patients whose notes records contained no explicit AD/dementia severity information, contained only qualitative AD/dementia severity or MMSE scores, or suggested a clinically unlikely progression (eg, severe to mild) were categorized as "unknown."

2.5 | Statistical analysis

Demographic characteristics were compared between patients with and without agitation using two-sample *t* tests for continuous

TABLE 1 Agitation identification: agitation terms consistent with the 2015 International Psychogeriatric Association Working Group agitation definition²⁷

Category	Example Symptoms
Excessive motor activity	Gesturing Finger pointing Irritability Jumpiness Pacing Repetitious mannerisms Repetitive questions/sentences Restlessness Rocking Shakiness Wandering
Verbal aggression	Complaining Constant requests for attention/neediness Excessively loud voice volume Negativism Outbursts Repetitions questions, statements Screaming Shouting Strange noises (unusual laughter, crying) Stubbornness Profanity/cursing/swearing Verbal sexual advances Yelling
Physical aggression	Biting Destruction of property Grabbing Hitting self or others Hoarding Hurting self or others Kicking Physical sexual advances Pushing Resistiveness Scratching Shoving Slamming doors Spitting Tearing objects Throwing objects

variables (with Satterthwaite approximation for unequal variances) and Pearson chi-squared tests for categorical variables. Outcomes were analyzed descriptively. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

3 | RESULTS

3.1 | Study sample and prevalence of agitation

The full study sample (Table 3) included 320 886 eligible patients (64.7% female); of these, 143 160 (44.6%) had EHR evidence of probable agitation during the 2-year observation period. In the preindex period, 63 092 (19.7%) of all study patients had at least one probable agitation notes record, and 4600 (1.4%) had a diagnosis code for AD/dementia with behavioral disturbance. Postindex, these numbers were 115 084 (35.9%) and 15 710 (4.9%). Only 2563 (0.8%) and 10 049 (3.1%) of all patients in the preindex and postindex periods, respectively, had both a probable agitation notes record and a diagnosis code for behavioral disturbance. Among the 143 160 patients with probable agitation, mean (standard deviation [SD]) counts of probable

TABLE 2 Alzheimer disease/dementia staging: criteria for assigning severity levels

Criteria	AD/Dementia Severity Level Assignment
Records containing a valid quantitative MMSE score	
MMSE score from 19 to 22	Mild
MMSE score from 12 to 18	Moderate
MMSE score ≤ 11	Severe
Records containing explicit terms of AD/dementia severity	
Terms such as "early" or "mild"	Mild
"Mild-to-moderate" (verbatim)	Mild-to-moderate
Terms such as "moderate"	Moderate
"Moderate-to-severe" (verbatim)	Moderate-to-severe
Terms such as "severe," "advanced," or "late-stage"	Severe
Patients whose notes records contained multiple severity levels	
Records containing both explicit severity level(s) and unknown severity level(s) (eg, mild and unknown or moderate and unknown)	Categorized as the explicit severity level
Records containing mild and moderate, mild-to-moderate and mild, or mild-to-moderate and moderate, in a sequence that suggested progression from mild to moderate	Mild-to-moderate
Records containing moderate and severe, moderate-to-severe and moderate, or moderate-to-severe and severe, in a sequence that suggested progression from moderate to severe	Moderate-to-severe
Other situations	
Records containing no explicit AD/dementia severity information	Unknown
Records containing only descriptive MMSE results or descriptions of AD/dementia severity (eg, "much better," "much worse," "stable," "within normal limits," "worsening," or "grossly abnormal")	Unknown
Records showing clinically questionable progression (eg, severe to mild)	Unknown

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental Status Examination.

TABLE 3 Patient characteristics

Characteristic	Total (n = 320 886)	Patients Without Agitation (n = 177 726)	Patients With Agitation (n = 143 160)	P Value
Age, years, mean (SD)	76.4 (5.2)	76.4 (5.2)	76.5 (5.2)	<0.001
Age category, years, n (%) ^a				0.001
65–74	104 743 (32.6)	58 433 (32.9)	46 310 (32.4)	
≥ 75	216 143 (67.4)	119 293 (67.1)	96 850 (67.7)	
Sex, n (%) ^a				0.067
Male	113 179 (35.3)	62 968 (35.4)	50 211 (35.1)	
Female	207 635 (64.7)	114 714 (64.5)	92 921 (64.9)	
Missing/unknown	72 (0.0)	44 (0.0)	28 (0.0)	
Preindex Charlson comorbidity score, mean (SD) ^b	1.3 (1.7)	1.1 (1.6)	1.5 (1.9)	<0.001

Abbreviation: SD, standard deviation.

^aPercentages may not sum to 100.0 because of rounding.

^bPreindex diagnosis records from which the Charlson comorbidity score could be computed were available for 287 327 patients (89.5%).

agitation notes records in the preindex and postindex periods were 2.3 (2.9) and 2.8 (4.0), respectively; and mean (SD) counts of diagnoses of AD/dementia with behavioral disturbances in the preindex and postindex periods were 2.3 (3.1) and 3.3 (5.6), respectively.

Mean (SD) age was 76.4 (5.2) years and was similar between patients without vs with agitation (76.4 [5.2] y vs 76.5 [5.2] y, respectively, $P < 0.001$; difference in mean age was not clinically meaningful but was statistically significant because of large sample size). Mean (SD) preindex Charlson comorbidity scores were 1.3 (1.7) in the full study sample, 1.1 (1.6) among patients without agitation, and 1.5 (1.9) among patients with agitation ($P < 0.001$ for patients without vs with agitation).

3.2 | Agitation symptoms

Among the 143 160 patients with agitation, the most prevalent agitation symptoms were agitation (31.4% preindex, 41.3% postindex), falling (22.6% preindex, 21.7% postindex), restlessness (18.3% preindex, 23.3% postindex), behavioral manifestations (16.0% preindex, 22.9% postindex), and shakiness (14.4% preindex, 13.6% postindex) (Figure 2).

Of the 320 886 eligible patients, 78 827 (24.6%) could be assigned to explicit AD/dementia severity categories. The prevalence of agitation in the staged subgroup was 61.3% (Table 4). The distribution of staged patients by AD/dementia severity level was as follows:

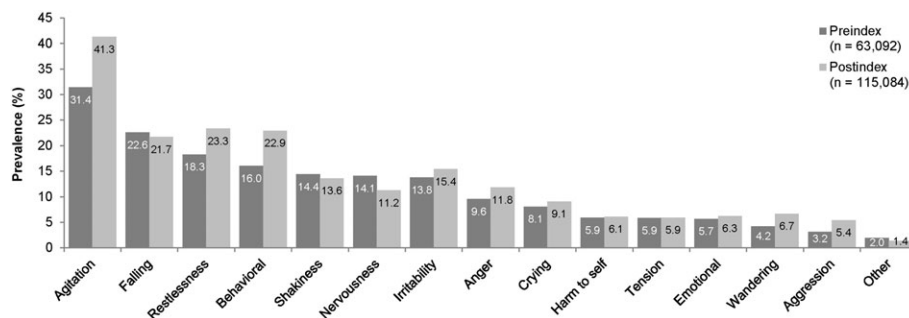


FIGURE 2 Preindex and postindex prevalence of agitation symptoms among patients with at least one probable agitation notes record

TABLE 4 Prevalence of agitation by Alzheimer disease/dementia severity level

Time Period	Total (n = 320 886)	All Staged Patients (n = 78 827)	Alzheimer Disease/Dementia Severity Level					
			Mild (n = 43 749)	Mild-to- moderate (n = 6712)	Moderate (n = 7856)	Moderate- to-severe (n = 3983)	Severe (n = 16 527)	Unknown (n = 242 059)
2-year observation period, n (%)	143 160 (44.6)	48 288 (61.3)	24 688 (56.4)	4392 (65.4)	4955 (63.1)	2973 (74.6)	11 280 (68.3)	94 872 (39.2)
12-month preindex	65 129 (20.3)	25 640 (32.5)	12 787 (29.2)	2125 (31.7)	2658 (33.8)	1552 (39.0)	6518 (39.4)	39 489 (16.3)
12-month postindex	120 725 (37.6)	40 533 (51.4)	20 284 (46.4)	3851 (57.4)	4230 (53.8)	2652 (66.6)	9516 (57.6)	80 212 (33.1)

mild, n = 43 749 (55.5%); severe, n = 16 527 (21.0%); moderate, n = 7856 (10.0%); mild-to-moderate, n = 6712 (8.5%); and moderate-to-severe, n = 3983 (5.1%). The percentages of patients with at least one record indicating agitation in the 2-year observation period were highest for patients with moderate-to-severe and severe AD/dementia (74.6% and 68.3%, respectively), followed by patients with mild-to-moderate and moderate AD/dementia (65.4% and 63.1%, respectively), and lowest for patients with mild AD/dementia (56.4%).

4 | DISCUSSION

Studies evaluating symptoms of agitation among patients with dementia are frequently conducted in a long-term care setting. To our knowledge, the present study is the first to use electronic health record data to estimate agitation prevalence among patients with dementia living in the community. In this large-scale analysis, the prevalence of agitation during the 2-year observation period was substantial: 44.6% in the full study sample and 61.3% in a subset of patients with staged AD/dementia severity. This constitutes not only a considerable strain on patient and caregiver health but also a considerable economic burden, as agitation has been shown to engender high additional costs compared with cognitive impairment alone.^{22,33} In a recent UK study, the presence of agitation was associated with significantly increased health care costs among home-dwelling patients with AD, accounting for mean excess costs of £2 billion per year.³³

Our agitation prevalence estimates fall within the 18% to 87% range described by a recent systematic review of previous studies on NPS in dementia.²⁸ Point prevalence rates for agitation/wandering and mechanical/motor abnormalities have previously been reported in

the range of 18% to 57%^{5,30} and 10% to 61%,^{5,34} respectively.^{5,6,10,35} The variation in reported rates may be attributable to methodological differences due to earlier studies defining NPS using the Neuropsychiatric Inventory (NPI), an assessment tool commonly used in clinical studies to screen for behavioral symptoms among patients with dementia.³⁶ First, while we identified agitation on the basis of EHR notes from direct physician encounters and available diagnosis codes, the NPI is conducted via an interview with the patient's primary caregiver, whose assessment of agitation may differ from that of a physician. Second, the degree to which items assessed in the NPI overlap with the IPA provisional definition of agitation is not clear. For example, the approximately 43% prevalence of agitation/aggression found among patients with AD by Steinberg et al⁴ over 5 years appears similar to the overall agitation prevalence in our patient population; however, anxiety (approximately 61%), irritability (approximately 57%), and aberrant motor behavior (approximately 52%) were assessed as separate items in the Steinberg et al study, making direct comparison difficult.

Notably, relatively few patients had a diagnosis code for behavioral disturbance in the EHR diagnosis table (1.4% preindex, 4.9% postindex) despite nearly 45% of the study population having notes records that referred to agitation during the observation period. Because the EHR diagnosis table is not used for billing, information in the table may not reflect claims submitted for payment. The lack of behavioral disturbance diagnosis codes observed in EHR may suggest that this symptom is underestimated in administrative claims data, which bolsters the argument for assessing symptoms using data from EHR in addition to claims. Not all conditions discussed between a physician and patient during an office visit will be coded on a claim,³⁷ and many conditions—including various agitation-related symptoms—do not have a specific ICD code, reducing the likelihood that they will be captured. Claims data therefore may not provide a

complete reflection of patient status.³⁸⁻⁴⁰ EHR data may capture signs and symptoms that are important to the clinical narrative but were not recorded as a diagnosis code, allowing the identification of patients that would have been missed by examination of claims data alone.³⁷

In the present study, agitation was most common among patients with moderate-to-severe and severe AD/dementia, with prevalence rates of 74.6% and 68.2%, respectively. Although evidence suggests that agitation is associated with poorer cognitive function^{20,28,35} and tends to increase over time,^{5,16,25,35} few previous studies have examined agitation prevalence by AD/dementia severity category. Our results are comparable with those of clinical studies by Lopez et al²⁹ and Khoo et al,³¹ who found that the prevalence of agitation rose with increasing cognitive impairment and was highest (67% and 71%, respectively) in those with severe dementia among community-dwelling patients. In contrast, other clinical studies have reported nonlinear relationships between cognitive status and agitation.^{30,41} Holtzer et al³⁰ found that mean MMSE scores among patients with probable AD decreased steadily over a 5-year follow-up, but the prevalence of agitation peaked at 57% in year 3 from a baseline level of 39% and then declined to 46% in year 5. A similar pattern was observed by Lovheim et al,⁴¹ who found that agitation symptoms such as wandering, aggression, restlessness, and verbally disruptive behavior were most prevalent among institutionalized patients in the middle stages of cognitive impairment. One possible explanation for these observations is that the diminished verbal ability and motor function associated with late-stage dementia may mask the manifestation of certain NPS among patients with advanced disease.⁴¹

Our assessment of agitation prevalence by AD/dementia severity was limited by the preponderance of unknown staging: Only 24.6% (78 827 of 320 886) of patients in the study sample could be assigned to explicit AD/dementia severity categories. This limitation is a source of potential confounding, as the observation that agitation was present among only 45% of the total study sample vs 61% of staged patients suggests that patients with notes records indicating AD/dementia severity may have been more likely to have documented agitation symptoms and that agitation may have been underreported in the total population. The insufficiency of notes records from our EHR database to evaluate AD/dementia severity for most patients is likely attributable to multiple reasons, including a lack of AD/dementia severity information in EHR notes, the inability of NLP to effectively capture the extent of variation in charting practices among physicians, and disparities in the volume and content of electronic notes available from provider organizations represented in the EHR database. In addition, only notes records from direct encounters between physicians and patients were examined in this study. As NLP often generates more than one notes record from a single full-text note and patients have notes records over time, there are multiple opportunities to identify a patient with a probable condition; nevertheless, some patients' severity status may have been missed because notes records from sources such as phone calls, emails, encounters with nonphysician health care providers, and interactions with caretakers were not interpreted.

Although the utilization of an EHR database to access diverse clinical information at large sample sizes was a strength of this study, the EHR data also have certain limitations that should be considered. Not every pertinent detail of a patient's health status will be reflected in EHR, and data for patients who receive some of their care from provider delivery organizations whose data are not included in the EHR database are incomplete. Furthermore, the EHR database contains data primarily from community-dwelling patients; therefore, mild or moderate AD/dementia is likely overrepresented and severe dementia underrepresented in the study sample, and the study findings cannot be generalized to residents of long-term care facilities. Given the potential incompleteness of EHR data, the lack of long-term care residents in the study population, and the fact that only EHR from direct physician encounters were evaluated, our analysis may underestimate the true prevalence of agitation in the total population of patients with AD/dementia. Finally, it is possible that patients with mild dementia may have been less likely to have a dementia severity categorization due to less frequent use of health care services, which may present fewer opportunities for severity evidence to show up in the EHR database. This scenario could have resulted in those with mild dementia being overrepresented among unstaged patients and underrepresented among staged patients, contributing to the lower prevalence of agitation observed for unstaged vs staged patients in the present study. However, it should be noted that the prevalence of agitation among staged patients in this analysis was comparable with that found in clinical studies in which dementia severity was determined via cognitive evaluation rather than from administrative claims or EHR data,^{29,31} suggesting that our results were not substantially affected by this potential bias.

5 | CONCLUSION

In this large sample of patients with AD/dementia, approximately 45% of all patients and nearly two-thirds of those whose AD/dementia severity could be determined had EHR documentation of agitation symptoms during the 2-year observation period. Among patients identified with agitation, only a small percentage had a diagnosis code for behavioral disturbance. The prevalence of agitation was highest among patients with moderate-to-severe and severe AD/dementia. While a majority of published studies have shown a high prevalence of agitation in the long-term care setting, this study indicates that agitation is also common among community-dwelling patients. Our findings underscore the importance of managing agitation in caring for patients with AD, particularly in light of the faster disease progression, poor quality of life, and high economic costs associated with this NPS. Furthermore, the possible undercoding of behavioral disturbance diagnoses in claims data suggests that the richer clinical data available in EHR should be utilized to study behavioral symptoms such as agitation in this population.

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CONFLICT OF INTEREST

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APPENDIX A

TABLE A1 Diagnosis codes for Alzheimer disease/dementia

Code	Type	Description
290.0	ICD-9-CM	Senile dementia, uncomplicated
290.10	ICD-9-CM	Presenile dementia, uncomplicated
290.11	ICD-9-CM	Presenile dementia with delirium
290.12	ICD-9-CM	Presenile dementia with delusional features
290.13	ICD-9-CM	Presenile dementia with depressive features
290.20	ICD-9-CM	Senile dementia with delusional features
290.21	ICD-9-CM	Senile dementia with depressive features
290.3	ICD-9-CM	Senile dementia with delirium
290.40	ICD-9-CM	Vascular dementia, uncomplicated
290.41	ICD-9-CM	Vascular dementia, with delirium
290.42	ICD-9-CM	Vascular dementia, with delusions
290.43	ICD-9-CM	Vascular dementia, with depressed mood
290.8	ICD-9-CM	Other specified senile psychotic conditions
290.9	ICD-9-CM	Unspecified senile psychotic condition
294.10	ICD-9-CM	Dementia in conditions classified elsewhere without behavioral disturbance
294.11	ICD-9-CM	Dementia in conditions classified elsewhere with behavioral disturbance
294.20	ICD-9-CM	Dementia, unspecified, without behavioral disturbance
294.21	ICD-9-CM	Dementia, unspecified, with behavioral disturbance
331.0	ICD-9-CM	Alzheimer disease
F0150	ICD-10-CM	Vascular dementia without behavioral disturbance
F0151	ICD-10-CM	Vascular dementia with behavioral disturbance
F0280	ICD-10-CM	Dementia in other diseases classified elsewhere without behavioral disturbance
F0281	ICD-10-CM	Dementia in other diseases classified elsewhere with behavioral disturbance
F0390	ICD-10-CM	Unspecified dementia without behavioral disturbance
F0391	ICD-10-CM	Unspecified dementia with behavioral disturbance
F05	ICD-10-CM	Delirium due to known psychological condition
G300	ICD-10-CM	Alzheimer disease with early onset
G301	ICD-10-CM	Alzheimer disease with late onset
G308	ICD-10-CM	Other Alzheimer disease
G309	ICD-10-CM	Alzheimer disease, unspecified

Abbreviations: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

TABLE A2 Diagnosis codes for non-Alzheimer dementia

Code	Type	Description
331.7	ICD-9-CM	Cerebral degeneration in diseases classified elsewhere
331.9	ICD-9-CM	Unspecified cerebral degeneration
G31.9	ICD-10-CM	Degenerative disease of nervous system, unspecified
331.3	ICD-9-CM	Communicating hydrocephalus
G91.0	ICD-10-CM	Communicating hydrocephalus
331.6	ICD-9-CM	Corticobasal degeneration
G31.85	ICD-10-CM	Corticobasal degeneration
G31.2	ICD-10-CM	Degeneration of nervous system due to alcohol
331.82	ICD-9-CM	Dementia with Lewy bodies
G31.83	ICD-10-CM	Dementia with Lewy bodies
331.11	ICD-9-CM	Pick disease
331.19	ICD-9-CM	Other frontotemporal dementia
G3101	ICD-10-CM	Pick disease
G3109	ICD-10-CM	Other frontotemporal dementia
333.4	ICD-9-CM	Huntington chorea
G10	ICD-10-CM	Huntington disease
G91.4	ICD-10-CM	Hydrocephalus in diseases classified elsewhere
G91.9	ICD-10-CM	Hydrocephalus, unspecified
331.5	ICD-9-CM	Idiopathic normal pressure hydrocephalus [INPH]
G91.2	ICD-10-CM	(Idiopathic) normal pressure hydrocephalus
G21.11	ICD-10-CM	Neuroleptic induced parkinsonism
331.4	ICD-9-CM	Obstructive hydrocephalus
G91.1	ICD-10-CM	Obstructive hydrocephalus
331.89	ICD-9-CM	Other cerebral degeneration
G21.19	ICD-10-CM	Other drug induced secondary parkinsonism
G91.8	ICD-10-CM	Other hydrocephalus
G21.8	ICD-10-CM	Other secondary parkinsonism
G31.89	ICD-10-CM	Other specified degenerative diseases of nervous system
332.0	ICD-9-CM	Paralysis agitans
332.1	ICD-9-CM	Secondary parkinsonism
G20	ICD-10-CM	Parkinson disease
G91.3	ICD-10-CM	Posttraumatic hydrocephalus, unspecified
331.81	ICD-9-CM	Reye syndrome
G93.7	ICD-10-CM	Reye syndrome
G21.2	ICD-10-CM	Secondary parkinsonism due to other external agents
G21.9	ICD-10-CM	Secondary parkinsonism, unspecified
331.2	ICD-9-CM	Senile degeneration of brain
G31.1	ICD-10-CM	Senile degeneration of brain, not elsewhere classified
G13.8	ICD-10-CM	Systemic atrophy primarily affecting central nervous system in other diseases classified elsewhere
G13.2	ICD-10-CM	Systemic atrophy primarily affecting the central nervous system in myxedema
G21.4	ICD-10-CM	Vascular parkinsonism

Abbreviations: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification.

TABLE A3 Electronic health record terms for agitation symptoms

Agitation Symptom	Electronic Health Record Term
Aggression	AGGRESSION
	AGGRESSIVE BEHAVIOR
	AGGRESSIVE PERSONALITY
Agitation	AGITATED
	AGITATED BEHAVIOR
	AGITATED DEPRESSION
	AGITATION
	PSYCHOMOTOR AGITATION
	RESTLESSNESS AND AGITATION
Anger	INTERMITTENT EXPLOSIVE OUTBURST
	ANGER
	ANGRY
Behavioral	ATTENTION SEEKING BEHAVIOR
	INAPPROPRIATE BEHAVIOR
	MANNERISM
	ABERRANT BEHAVIOR
	ABNORMAL BEHAVIOR
	ANTISOCIAL BEHAVIOR
	BEHAVIOR
	BEHAVIOR ABNORMALITY
	BEHAVIOR CHANGES
	BEHAVIOR DISORDER
	BEHAVIOR IMPAIRED
	BEHAVIOR ISSUES
	BEHAVIORAL
	BEHAVIORAL ABNORMALITY
	BEHAVIORAL CHANGES
	BEHAVIORAL IMPAIRED
	BEHAVIORAL ISSUES
	CHANGE IN BEHAVIOR
	DELINQUENT BEHAVIOR
	DISRUPTIVE BEHAVIOR DISORDER
	DISTURBANCE IN PHYSICAL BEHAVIOR
	HYPOMANIC BEHAVIOR
	IMPULSIVE BEHAVIOR
	MANIC BEHAVIOR
	NON-SELF-REGULATORY BEHAVIOR
	ODD BEHAVIOR
	STRANGE BEHAVIOR
	UNABLE TO CONTROL BEHAVIOR
	VERBALLY ABUSIVE BEHAVIOR
	WEIRD BEHAVIOR
WEIRDNESS	
Cooperation	LACK OF COOPERATION
	LACK OF PATIENT COOPERATION
Crying	CRYING
	CRYING SPELLS
Emotional	DISTRESS
	EMOTIONAL CRISIS
	EMOTIONAL INSTABILITY
	EMOTIONAL ISSUES

(Continues)

TABLE A3 (Continued)

Agitation Symptom	Electronic Health Record Term	
	EMOTIONAL LABILITY	
	EMOTIONAL STRESS	
	EMOTIONAL UPSET	
	EMOTIONALLY LABILE	
	ACCIDENTAL FALL	
Fall	FALL	
	FALL DOWN STAIRS	
	FALL DOWN STEPS	
	FALL FROM BED	
	FALL FROM CHAIR	
	FALL FROM HEIGHT	
	FALL FROM SLIPPING	
	FALL FROM STAIRS	
	FALL FROM STANDING HEIGHT	
	FALL FROM STOOL	
	FALL FROM TOILET SEAT	
	FALL FROM WHEELCHAIR	
	FALL IN BATHTUB	
	FALL IN HOME	
	FALL IN NURSING HOME	
	FALL IN SHOWER	
	FALL ON CONCRETE	
	FALL ON ICE	
	FALL ON SNOW	
	FALL ON STAIRS	
	FALL ON STEPS	
	FALL RISK	
	FALLS	
	MECHANICAL FALL	
	Hostility	HOSTILE
		HOSTILE BEHAVIOR
		HOSTILITY
	Irritability	IRRITABILITY
		IRRITABILITY AND ANGER
		IRRITABLE
Jumpy	IRRITATION	
	EDGY	
	JITTERY	
	JUMPY	
	UNABLE TO KEEP STILL	
	NERVOUS	
Nervous	NERVOUSNESS	
	EXCESSIVE SPITTING	
Other	MULTIPLE COMPLAINTS	
	MULTIPLE SOMATIC COMPLAINTS	
	NAIL BITING	
	NEGATIVISM	
	RESISTANCE TO CHANGE	
Harm to others	SEXUAL ISSUES	
	HITTING	
	VIOLENCE	

(Continues)

TABLE A3 (Continued)

Agitation Symptom	Electronic Health Record Term
Restless	MOTOR RESTLESSNESS
	RESTLESS
	RESTLESSNESS
Harm to self	HARM SELF
	SELF-ABUSIVE
	SELF-ABUSIVE BEHAVIOR
	SELF-CUTTING
	SELF-DESTRUCTIVE
	SELF-DESTRUCTIVE BEHAVIOR
	SELF-INJURIOUS BEHAVIOR
	SELF-INJURY
Shakiness	SELF-MUTILATION
	SHAKES
	SHAKINESS
	SHAKING
Tension	SHAKING ALL OVER
	TENSE
	TENSENESS
Wandering	TENSION
	WANDER
	WANDERERS
	WANDERING
	WANDERS
	WANDERS AT NIGHT