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The Impact and Unmet Needs Associated With Dementia-Related Psychosis

- Dementia is a major cause of disability in the later stages of life,¹ and the number of Americans living with dementia appears to be increasing, potentially because the prevalence of dementia increases with age and the population of older adults in the United States is increasing.^{2,3}
- Hallucinations and/or delusions, 2 of the neuropsychiatric symptoms of dementia,⁴ are associated with worse patient outcomes, including institutionalization and death.⁵
- There are no FDA-approved atypical antipsychotics for the treatment of dementia-related psychosis,⁶ and clinical compendia recognized by CMS do not recognize the use of atypical antipsychotics as medically acceptable treatment for dementia-related psychosis.⁷
- Because of the prevalence and burden associated with dementia-related psychosis and the anticipated growth of the condition in the near future, there remains a critical unmet need for effective pharmacologic therapy for dementia-related psychosis.

Dementia is a syndrome caused by diseases of the brain and typically results in progressive decline in various aspects of intellect such as memory, language, comprehension, learning, and judgment.¹ Common signs of dementia include memory loss that alters daily life, difficulty in planning or problem-solving, inability to finish familiar tasks, confusion about time, place, or both; and changes in mood or personality.⁸ This syndrome is a major cause of disability in the later stages of life.¹

The number of Americans living with dementia appears to be increasing, potentially because the prevalence of dementia increases with age and the US older adult population is increasing.^{2,3} Dementia was present in an estimated 3.4 million adults aged 71 years and older in 2000, whereas estimates for adults 65 years and older with dementia rose to approximately 4.3 million in 2012.⁹⁻¹¹ In 2014, approximately 5.0 million individuals (ie, 1.6% of the US population) aged 65 years and older were believed to be living with dementia in the United States.¹² Furthermore, data from the 2015 National Health and Aging Trends Study indicate that although the prevalence of dementia among community-dwelling older adults in the United States in 2015 was 2% for those aged 65 to 69 years, that number increased to 33% among adults 90 years and older.¹³

This growth in the number of patients with dementia is expected to continue in the coming decades. For example, by 2050, the predicted number of Americans 65 years or older with Alzheimer disease, the most common cause of dementia in older adults, is expected to be 13.8 million.^{2,11}

THE BURDEN OF DEMENTIA AND NEUROPSYCHIATRIC SYMPTOMS

There are various types of neurodegenerative dementias, including Alzheimer disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, and Parkinson disease dementia.^{1,14,15} Despite the discovery of these dementia types, their accurate diagnosis remains difficult in clinical practice, in part because of mixed pathologies within patients. Analysis of post-mortem pathology data from 2 large databases found a large degree of overlap in neuropathology, regardless of age at the time of death.¹⁵ More than half of the patients with dementia (59% from

1 database and 68% from the other) exhibited mixed neuropathologies (ie, Alzheimer disease neuropathologic change with Lewy body disease or with vascular brain injury characterized as gross infarcts and cortical microinfarcts).¹⁵

The difficulty in making a definitive diagnosis of a specific dementia type in the clinic is also evident by the use of nonspecific diagnostic codes. The results of a retrospective study of a large administrative claims database with data from 12,047 patients 40 years or older (January 2009 through March 2017), presented at the ISPOR 2019 conference, May 18-22, 2019, in New Orleans, Louisiana, showed that more than 50% of patients had nonspecific dementia diagnostic codes, either senile/presenile dementia (27.9%) or unspecified dementia (27.2%). A total of 14.8% of patients had no dementia diagnosis despite receiving treatment for the condition.¹⁶

Although the type of provider appears to differ according to the patient's setting, dementia is often managed by primary care providers (PCPs) rather than specialists. A 2016 cross-sectional analysis of 2012 data of more than 2.5 million Medicare beneficiaries with a diagnosis of dementia found that the majority of beneficiaries in long-term care (> 90%) and the community (77%) were treated by primary care ($P < .001$) (Figure 1¹⁷). After PCPs, the predominant provider of ambulatory care for patients in the community were specialists (11.1%) in cardiology, neurology, hematology/oncology, and urology, followed by neurologists (3.8%) and psychiatrists (0.6%) ($P < .001$ for all). In contrast, psychiatrists more frequently served as the predominant provider of ambulatory care (after PCPs) for patients in long-term care (2.0%), followed by specialists (1.3%) in cardiology, neurology, hematology/oncology, and urology, and neurologists (0.3%) ($P < .001$ for all).¹⁷

In 2019, the Alzheimer's Association surveyed PCPs to better understand their perspectives on their roles in the treatment of patients with dementia. Of those PCPs surveyed, 82% indicated that they felt that they were "on the front lines" of treating dementia in their patients, and 53% reported receiving questions about dementia from patients 65 and older and their caregivers "every few days or more."

Despite this frequency of encounters with dementia, 50% of PCPs reported feeling that the medical profession as a whole is not fully prepared to treat the increasing number of patients with dementia. Thirty-two percent of PCPs reported referring at least 1 patient with dementia per month to a specialist; however, 55% stated that the number of specialists needed to address patient demand in their location was inadequate.⁸

The need for specialists to treat patients with dementia is expected to grow in the near future. Estimates indicate that the current number of geriatricians in the United States is approximately half what is required to address the needs of those with Alzheimer disease. By 2025, the United States is expected to require 19% more neurologists to meet this growing need, and by 2050, the number of geriatricians will need to increase nearly 200% to manage the number of patients with Alzheimer disease.¹⁸

MANAGEMENT OF DEMENTIA AND NEUROPSYCHIATRIC SYMPTOMS

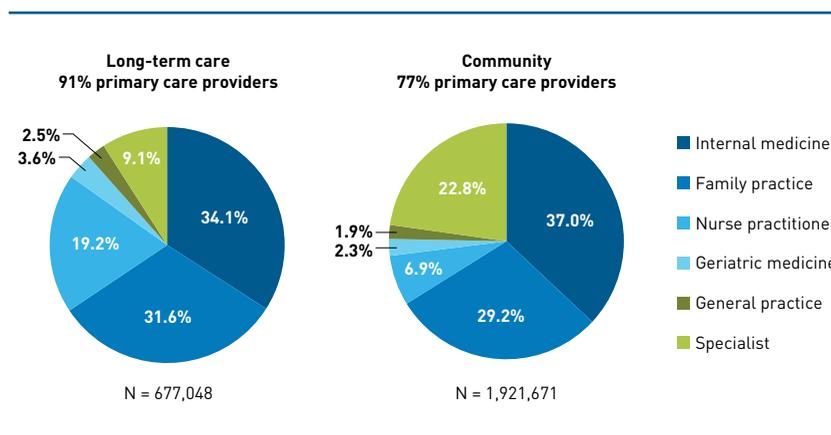
The Neuropsychiatric Inventory (NPI) can be used to measure neuropsychiatric symptom domains in the management of dementia. Two types of NPI—the 10-item NPI and 12-item NPI—have been developed: both are used to assess patients for delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior; however, the 12-item NPI is also used to evaluate patients for disturbances in nighttime behavior and in appetite or eating behavior.^{19,20} An NPI score is based on the frequency and severity scores for each neuropsychiatric domain, as rated by a patient's caregiver. The maximum total score that can be reached on the 12-item NPI is 144.²¹

Neuropsychiatric symptoms evaluated by the NPI are common to various types of dementia; the cumulative 5-year prevalence of at least 1 neuropsychiatric symptom in community-dwelling patients with dementia is 97%.²² An increase in neuropsychiatric symptoms (ie, an increase in NPI score) is correlated with an increase in nursing home admission. In a 2016 case-control study of data from the South Carolina Alzheimer's Disease Registry, a 10% increase in the total NPI score was associated with a 30% increase in the odds of nursing home placement ($n = 352$ patients with Alzheimer disease [mean age, 84.15 years] who entered a nursing home within 6 months of the study; $n = 289$ control subjects [mean age, 83.13 years] in the community) (odds ratio [OR], 1.30; 95% CI, 1.14-1.50).²³

The results indicated that the following NPI items were associated with a significant increase in the odds of nursing home placement²³:

- delusions (OR, 1.10; 95% CI, 1.03-1.19)
- irritability (OR, 1.10; 95% CI, 1.03-1.18)
- disinhibition (OR, 1.18; 95% CI, 1.07-1.29)

Figure 1. Medicare Beneficiaries With Dementia Are Primarily Managed in Primary Care¹⁷



- agitation/aggression (OR, 1.10; 95% CI, 1.06-1.23)
- sleep (OR, 1.12; 95% CI, 1.05-1.19)
- appetite (OR, 1.10; 95% CI, 1.02-1.18)

Hallucinations, aberrant motor behavior, depression, anxiety, elation, and apathy were not significantly associated with an increase in odds of nursing home placement.²³

ECONOMIC BURDEN OF DEMENTIA AND NEUROPSYCHIATRIC SYMPTOMS

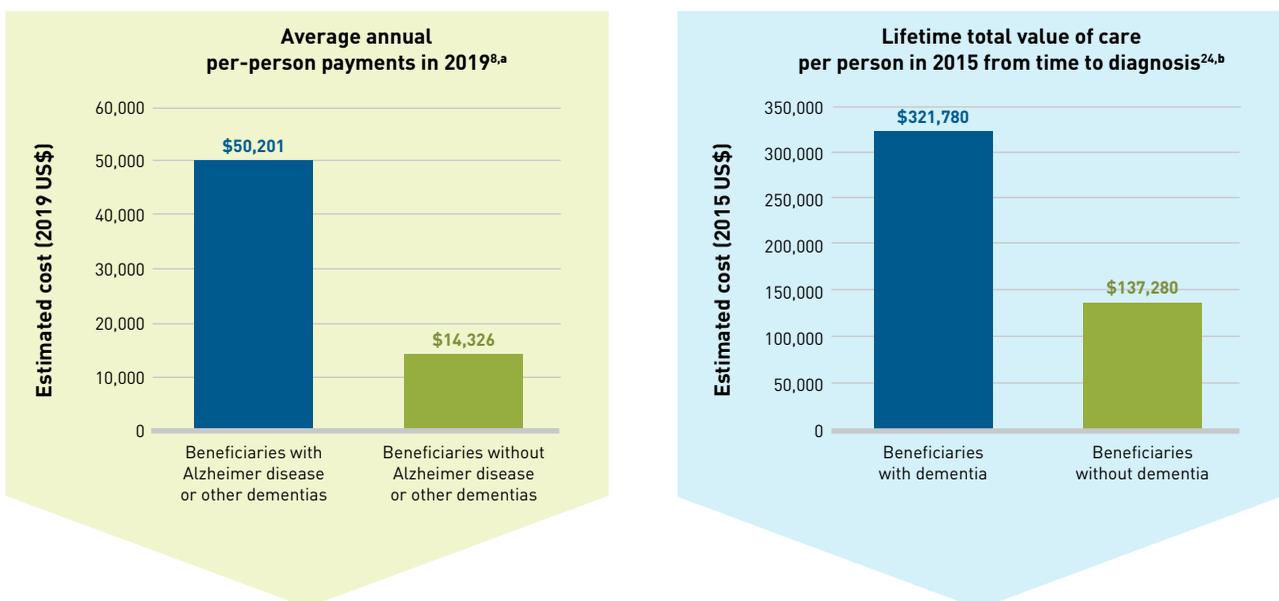
The economic burden associated with dementia is substantial, and the annual and lifetime care costs for patients with dementia far exceed those of individuals without dementia (Figure 2^{8,24}). The results of a 2017 study found that the mean discounted lifetime total value of care for a person with dementia was estimated at \$184,500 (2015 US\$) more than that for a person without dementia.²⁴ Additionally, the results of a 2019 health care resource utilization study of a large US administrative claims database found that the mean annual all-cause costs were much greater among patients with dementia-related psychosis during the 12 months after a psychosis event than during the 12 months before it (\$21,706 vs \$14,038, respectively) (n = 12,047).¹⁶ In 2020, the Alzheimer’s Association reported that the average annual per-person payment (2019 US\$) to beneficiaries 65 years and older was more than 3 times greater for those with dementia than for those without.⁸

An increase in the cost of care for patients with dementia has also shown to be correlated with an increase in NPI score. According to investigators on the Cache County Dementia Progression Study, which looked at the relationship between cost of informal caregiving and neuropsychiatric symptoms in 280 patients with dementia (72.1% with Alzheimer disease), increases in the severity of neuropsychiatric symptoms—as indicated by increases in the total NPI score and subdomain scores—predicted increases in the informal caregiving expenditure (2015 US\$). For each unit increase in NPI total score, the informal cost of care increased by 2%. Informal cost of care increased by 7.6% with each unit increase in the NPI subdomain of agitation/aggression (P = .030), by 6.4% with each unit increase in affective symptoms (P < .001), and by 5.6% with each unit increase in hallucinations and delusions (P = .005).²¹

CAREGIVER BURDEN OF DEMENTIA AND NEUROPSYCHIATRIC SYMPTOMS

In addition to cost, dementia-related neuropsychiatric symptoms can negatively affect caregivers. Results of the 2001 Canadian Study of Health and Aging showed that the burden for informal caregivers of 326 community-dwelling older adults with dementia was significantly associated with not only the patient’s behavioral disturbance (measured by the Dementia Behavior Disturbance scale) but also the caregiver’s depressive mood (r = 0.55). Caregiver burden was assessed

Figure 2. Annual and Lifetime All-Cause Health Care Costs in Patients With Dementia Far Exceed Those for Individuals Without Dementia^{8,24}



^a2011 data from a Medicare database, inflated to 2019 US\$. Payments from sources do not equal total payments exactly due to the effects of population weighting. Payments for all beneficiaries with Alzheimer disease or other dementias include payments for community-dwelling and facility-dwelling beneficiaries.

^bData from Medicare and Medicaid databases.

through the Zarit Burden Interview (ZBI), a 22-item questionnaire from which a total score of 88 can be calculated. The results of the ZBI indicated that severity of caregiver burden was associated with a higher adjusted odds of institutionalization. Patients whose informal caregivers reported a moderate burden (score: 9-17) were about 1.6 times more likely to be institutionalized (95% CI, 0.69-3.99), whereas those who reported a severe burden (score: 18-32) were about 3 times more likely to be institutionalized (95% CI, 1.34-7.59), and those who reported an extreme burden (score: 33-88) were almost 8.4 times more likely to be institutionalized (95% CI, 3.44-22.04).²⁵

Furthermore, professional caregivers experience a substantial burden in their work with patients with dementia and neuropsychiatric symptoms. The results of a 2019 meta-analysis of 17 studies that examined workers caring for patients with dementia in long-term care settings found that 22.1% to 68.6% of workers reported high levels of emotional exhaustion.²⁶ Caring for residents with agitated behavior was noted as a determinant of burnout, and 75% of caregivers in 1 study described residents as having “emotional difficulties.”^{26,27}

Multiple measures of psychiatric and behavioral symptoms of adults with dementia are associated with increased levels of caregiver burden, depression, and distress. A 2010 analysis of data from the Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer’s Disease (CATIE-AD) study examined the relationship between neuropsychiatric symptoms in 421 ambulatory patients with Alzheimer disease and hallucinations and delusions or agitation, and the burden, depression, and distress of their caregivers. To assess neuropsychiatric symptoms of patients with dementia, the investigators used the Brief Psychiatric Rating Scale (BPRS) and the NPI. Mood symptoms in patients with dementia were assessed with the Cornell Scale for Depression in Dementia (CSDD). Caregiver burden was measured with the Burden Interview, caregiver depression was assessed with the Beck Depression Inventory, and caregiver distress was determined with the Caregiver Distress Scale. Both neuropsychiatric symptoms (as measured with the NPI and BPRS) and mood symptoms (as measured with the CSDD) of the patients with dementia were significantly correlated with the scores on the Burden Interview, the Beck Depression Inventory, and the Caregiver Distress Scale ($P < .001$ for each).²⁸

The negative impact of neuropsychiatric symptoms on the lives of the patients with dementia and their caregivers also was assessed in a 2020 observational, noninterventional, prospective study. Qualitative interviews of 15 caregivers and 1 patient identified visual hallucinations (~88%), auditory hallucinations (~69%), and persecutory delusions (~56%) as the most commonly reported symptoms. Symptoms of dementia-related psychosis affected activities of daily living (75% of respondents), sleep (~63%), family life (~56%), and safety (~56%). In the quantitative part of the study, which included 26 patients and 186 caregivers, the most frequently reported symptoms differed between patients and caregivers. Patients more frequently reported visual hallucinations (~89%), auditory hallucinations (~54%), and sense distortion (~54%), whereas caregivers most often reported the patient as experiencing paranoid delusions (~76%), visual hallucinations (~75%), and a lack of trust for a loved one (~52%). Patients

noted their most impactful symptom to be visual hallucinations, whereas paranoid delusions/false beliefs (from the patient) were noted to be most impactful to the caregivers.²⁹

IMPACT OF HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH DEMENTIA-RELATED PSYCHOSIS

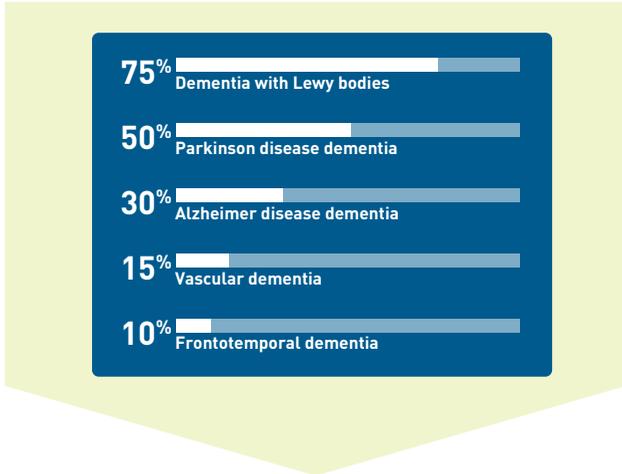
The phrase “neuropsychiatric symptoms” covers a variety of symptoms, 2 of which are hallucinations and delusions. The *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* defines hallucinations as “perception-like experiences that occur without an external stimulus” and are sensory in nature (ie, they may be auditory, visual, olfactory, gustatory, or tactile).⁴ In patients with dementia, the most common hallucinations are visual or auditory.³⁰ Distinct from hallucinations, delusions are false, fixed beliefs despite evidence to the contrary.⁴ The most commonly reported types of delusions in patients with dementia include delusions of reference, which is the belief that a neutral event has a special meaning especially for them, or delusions of theft.⁴ Other delusions include delusional misperceptions (eg, television and photograph misperceptions); Capgras syndrome (ie, the belief that a person, usually a family member, has been replaced by an impostor); delusional misperceptions of the house or other objects; and delusions of uninvited strangers in the home, also known as a phantom boarder delusion.^{30,31}

The estimated prevalence of hallucinations and delusions associated with dementia-related psychosis varies across dementia types (Figure 3^{14,30,32-44}). For example, these symptoms are experienced by 75% of patients with dementia with Lewy bodies,^{14,32-34} 50% with Parkinson disease dementia,^{14,32,35} 30% with Alzheimer disease dementia,^{32,33,36-42} 15% with vascular dementia,^{32,36-38} and approximately 10% of patients with frontotemporal dementia.^{43,44}

In a 2000 study, Jeste and Finkel proposed diagnostic criteria for psychosis in patients with Alzheimer disease. These criteria were intended by the authors to distinguish symptoms of psychosis with Alzheimer disease from those seen with delirium (although they can coexist for a time), other medical conditions, primary psychiatric conditions (eg, schizophrenia), and drug abuse. These criteria, which follow, may also apply to psychosis with other dementia types (Table⁴⁵).

Dementia-related psychosis is related to an increase in behavioral, psychological, and cognitive problems. The results of a 1996 analysis of information from a database of 9 Alzheimer disease diagnosis and treatment centers in California identified 101 patients with Parkinson disease dementia. Those patients with hallucinations and/or delusions ($n = 36$) had significantly greater rates of insomnia, confusion, agitation, and self-care problems than patients without hallucinations or delusions ($P \leq .05$ for each comparison). In addition, cognitive or functional scores, as measured by the Blessed Information-Memory-Concentration Test, Blessed-Roth Dementia Rating Scale, and Mini-Mental State Examination indicated significantly greater rates of cognitive and functional impairment among those with hallucinations and/or delusions ($P \leq .005$ for each) (Figure 4).⁴⁶

Figure 3. Estimated Prevalence of Hallucinations and Delusions Associated With Dementia-Related Psychosis Among the 5 Most Common Dementia Types in the United States^{14,30,32-44}



Evidence suggests that dementia-related hallucinations and delusions may be associated with aggression among patients who live in the community or long-term care facilities; however, the relationship is complex. The results of a 12-month study of 270 community-dwelling patients in 1997 with probable Alzheimer disease (128 participants had experienced delusions and 99 participants had experienced hallucinations at baseline) showed that after controlling for dementia severity and previous episodes of aggression, among those individuals with Alzheimer disease and delusions, the relative risk (RR) of physical aggression increased 2.8-fold (RR, 2.8; 95% CI, 1.3-4.3; $P = .009$). Hallucinations were not found to increase the relative risk of physical aggression in this study (RR, 1.2; 95% CI, 0.3-2.7; $P = .653$).⁴⁷

Hallucinations and delusions were both associated with an increased odds of aggression based on the results of a 2003 study that assessed the relationship between psychiatric syndromes and dementia severity in 1155 people diagnosed with probable Alzheimer disease (moderate Alzheimer disease: OR, 2.35; 95% CI, 1.78-3.06; severe Alzheimer disease: OR, 11.1; 95% CI, 8.4-14.4).⁴⁰

The presence of dementia-related hallucinations and delusions also was found to increase the likelihood of physical aggression among patients who live in long-term care facilities. The results of a large 2006 study of long-term care residents with dementia (N = 103,344) found that approximately 7% (n = 7120) had reportedly been aggressive in the week prior to their annual comprehensive health assessment. The presence of hallucinations and delusions significantly increased the odds of physical aggression among residents with dementia after adjusting for potential confounders (eg, age, sex, severity of cognitive impairment). Hallucinations were associated with a 1.4-fold increase in the odds of physical aggression

TABLE. Proposed Diagnostic Criteria for Psychosis of Alzheimer Disease⁴⁵

A. Characteristic Symptoms	
Presence of 1 (or more) of the following symptoms:	
1. Visual or auditory hallucinations	
2. Delusions	
B. Primary Diagnosis	
All the criteria for dementia of the Alzheimer type are met ^a	
C. Chronology of the onset of symptoms of psychosis vs onset of symptoms of dementia	
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia	
D. Duration and Severity	
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning.	
E. Exclusion of schizophrenia and related psychotic disorders	
Criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Mood Disorder With Psychotic Features have never been met	
F. Relationship to delirium	
The disturbance does not occur exclusively during the course of a delirium	
G. Exclusion of other causes of psychotic symptoms	
The disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (eg, a drug of abuse, a medication)	
Associated features: (<i>Specify if associated</i>)	
With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression	
With Negative Symptoms: when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present	
With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present	
^a For other dementias, such as vascular dementia, Criterion B will need to be modified appropriately.	

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(OR, 1.4; 99% CI, 1.1-1.8), whereas delusions were associated with a 2-fold increase (OR, 2.0; 99% CI, 1.7-2.4).⁴⁸

Hallucinations and/or delusions in patients with dementia may be associated with worse outcomes, including institutionalization and death. The results of a 2005 multicenter cohort study of 456 patients with probable Alzheimer disease and up to 14 years of follow-up

(mean, 4.5 years) determined that both hallucinations and delusions were significantly associated with an increased risk of cognitive decline (RR, 1.62 [95% CI, 1.06-2.47] and 1.50 [95% CI, 1.07-2.08], respectively) and functional impairment (RR, 2.25 [95% CI, 1.54-3.27] and 1.41 [1.02-1.94]). In this study, hallucinations, but not delusions, were significantly associated with institutionalization (RR, 1.60 [95% CI, 1.13-2.28]) and death (RR, 1.49 [95% CI, 1.03-2.14]).⁵

Similar findings were seen in the 2015 population-based Cache County Dementia Progression Study that followed 335 individuals 65 years or older with incident cases of possible or probable Alzheimer disease. Reassessment occurred at intervals of 3 to 5 years (mean = 3.53 years [SD = 0.6]). Within this sample, individuals with dementia-related hallucinations and delusions were 2 times more likely to progress to severe dementia (HR, 2.0; $P = .03$) and 1.5 times more likely to progress to death (HR, 1.5; $P = .01$).⁴⁹

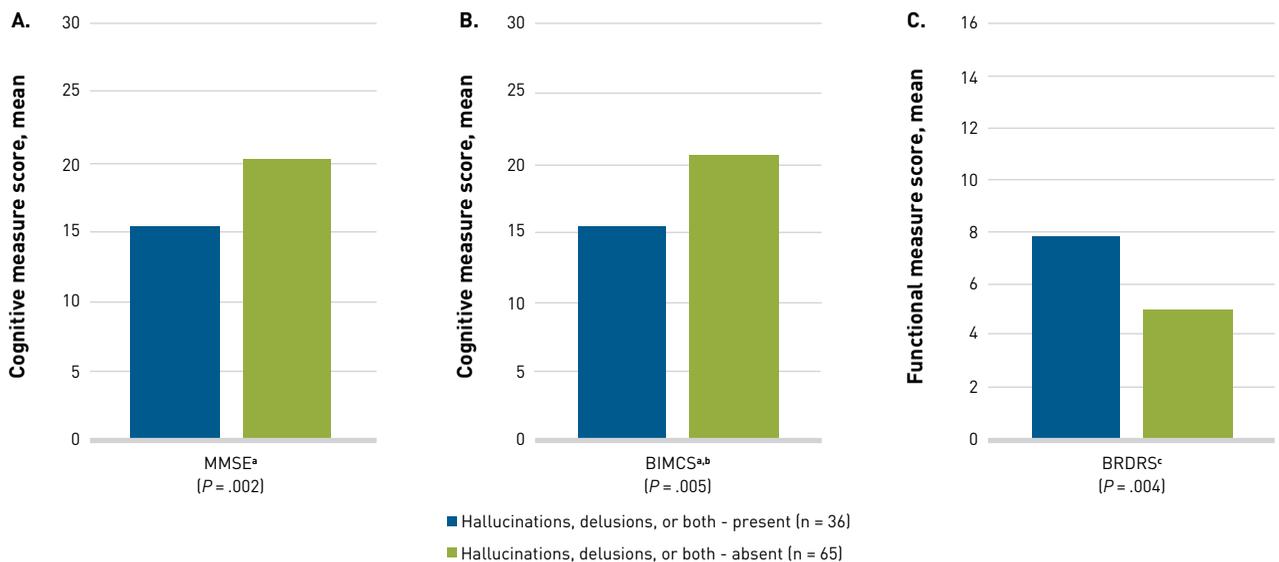
UNMET NEED IN TREATMENT OF HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH DEMENTIA-RELATED PSYCHOSIS

When dementia-related psychosis is diagnosed, medications that are not FDA approved for this condition are sometimes used for

treatment. The results of a 2020 analysis of anonymous patient level data from a third-party longitudinal claims database estimated that approximately 700,000 patients with dementia and psychotic symptoms were prescribed an antipsychotic, and an additional 100,000 were prescribed a mood stabilizer.⁵⁰ Furthermore, the results of a retrospective cohort study that used data on adult long-term care and residents with dementia (mean age, 82.7; January 1, 2013, to May 30, 2017) found that of the 26,002 residents with dementia, 11,921 had dementia-related psychosis.⁵¹ Of those with dementia-related psychosis, 94.3% ($n = 11,246$) were prescribed antipsychotics and/or mood stabilizers, neither of which were approved for the treatment of hallucinations and delusions due to dementia-related psychosis.^{6,51}

Evidence from clinical trials indicate that off-label use of antipsychotic therapy for dementia-related psychosis can lead to serious adverse events (AEs). In 2005, the FDA conducted an analysis of 17 placebo-controlled trials placebo-controlled trials in elderly patients with behavioral disorders ($n = 5106$) and determined that there was an approximate 1.6- to 1.7-fold increase in mortality in elderly patients with dementia-related psychosis given atypical antipsychotics compared with those given a placebo.⁶ Most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Because of these findings, the FDA currently requires all antipsychotic medications to carry a boxed warning indicating that

Figure 4. Cognitive or Functional Measure Scores of Patients With Parkinson Disease Dementia, With or Without Hallucinations and/or Delusions⁴⁶



BIMCS, Blessed Information-Memory-Concentration Test; BRDRS, Blessed-Roth Dementia Rating Scale; MMSE, Mini-Mental State Examination.

^aLower score indicates greater dysfunction.

^bNumber of correct responses.

^cHigher score indicates greater dysfunction.

Adapted from Naimark D, Jackson E, Rockwell E, Jeste DV. *J Am Geriatr Soc.* 1996;44(3):296-299. doi:10.1111/j.1532-5415.1996.tb00918.x

elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Moreover, the clinical compendia recognized by CMS (ie, the American Hospital Formulary Service Drug Information and DRUGDEX Information System) do not consider the off-label use of atypical antipsychotics as a “medically accepted” treatment for dementia-related psychosis.⁷

Following the FDA analysis, in 2006, Schneider and colleagues conducted an independent, individual study-based meta-analysis of 15 placebo-controlled clinical trials of atypical antipsychotics to assess the evidence for their efficacy and safety in patients with dementia.⁵² The analysis revealed inconsistent evidence of efficacy for the treatment of behavioral and psychological symptoms in patients with dementia. In addition, when compared with placebo, the use of atypical antipsychotics in patients with dementia was associated with a significantly greater risk of AEs, including somnolence (OR, 2.84; 95% CI, 2.25-3.58; $P < .00001$), extrapyramidal effects (OR, 1.51; 95% CI, 1.20-1.91; $P = .0005$), abnormal gait (OR, 3.42; 95% CI, 1.78-6.56; $P = .0002$), edema (OR, 1.99; 95% CI, 1.20-3.30; $P = .008$), urinary tract infection (OR, 1.28; 95% CI, 1.02-1.61; $P = .04$), and cerebrovascular events (OR, 2.13; 95% CI, 1.20-3.75; $P = .009$). The increased risk of death (OR, 1.54; 95% CI, 1.06-2.23; $P = .02$) was consistent with the finding from the FDA analysis.^{52,53}

Also in 2006, Schneider and colleagues conducted CATIE-AD, a double-blind, placebo-controlled study of the efficacy and safety/tolerability of atypical antipsychotics in outpatients with Alzheimer disease and psychosis, aggression, or agitation severe enough to warrant the use of antipsychotics. For phase 1 of the study, patients were randomly assigned to atypical antipsychotics or placebo ($n = 421$; mean age 77.9 years). Doses could be adjusted as clinically indicated, and treatment could be continued for up to 36 weeks or discontinued after the first 2 weeks if the response was inadequate. Patients whose initial treatment was discontinued ($n = 253$) could be enrolled in phase 2. These patients were randomly assigned to receive an antipsychotic to which they were not initially assigned or citalopram.⁵⁴

Overall, none of the treatment groups differed significantly in the time to discontinuation for any reason (primary end point) or in response rate at 12 weeks (main secondary end point).⁵⁴ The overall rate of discontinuation at 12 weeks was relatively high (63%), and the rates of discontinuation because of AEs ranged from 16% to 24%, depending on the atypical antipsychotic (vs 5% with placebo; $P = .009$ for overall comparison). The inconsistent efficacy and substantial frequency of AEs, including an increased risk of death, observed with the off-label use of atypical antipsychotics in the treatment of dementia-related psychosis were also recorded in other studies.⁵⁵⁻⁵⁷

GUIDELINE RECOMMENDATIONS ON TREATMENT OF DEMENTIA-RELATED PSYCHOSIS

To assist physicians in the use of antipsychotics for the treatment of dementia-related psychosis or agitation, the American Psychiatric Association (APA) issued practice guidelines.⁵⁸ Based on its review of the published evidence, the APA recommends that nonemergency

antipsychotic medication be used when the agitation or psychosis is severe, the patient is dangerous, and/or the symptoms are causing the patient substantial distress. Before an antipsychotic is used in a nonemergency situation, the patient’s clinical response to nonpharmacologic measures should be reviewed, and the potential risks and benefits of an antipsychotic should be discussed with the patient and/or caregiver. It is noteworthy that the APA indicated that the overall strength of evidence supporting the use of atypical antipsychotics for dementia-related psychosis is low.⁵⁹

The American Geriatric Society updated the Beers Criteria for potentially inappropriate medication use in older adults in 2019 and recommended that antipsychotics, whether used long term or as needed, be avoided for the treatment of behavioral symptoms of dementia unless nonpharmacologic interventions have been unsuccessful or the patient is at risk of harming themselves or others.⁶⁰ Greater risks of stroke and mortality are part of the rationale for avoiding antipsychotic use in patients with dementia-related psychosis.⁶⁰ In general, older persons with dementia often have specific vulnerabilities, such as multiple comorbidities and polypharmacy, that health care professionals should consider when devising a treatment regimen.⁶¹

CONCLUSIONS

Dementia-related psychosis poses a substantial burden to patients and their caregivers and is associated with increases in health care costs, progression to severe dementia, institutionalization, cognitive worsening, and death. Although atypical antipsychotics are sometimes used to treat dementia-related psychosis, their efficacy has been shown to be inconsistent, and the AEs associated with their use are substantial. There are no FDA-approved atypical antipsychotics for the treatment of dementia-related psychosis, and the prescribing information for all atypical antipsychotics has a boxed warning for an increased risk of death in elderly patients with dementia-related psychosis. Moreover, clinical compendia recognized by the CMS do not recognize the use of atypical antipsychotics as medically acceptable treatment for dementia-related psychosis. Because of the prevalence and burden associated with dementia-related psychosis and the anticipated growth of the condition in the near future, there remains a critical unmet need for effective pharmacologic therapy for dementia-related psychosis. •

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Expert Perspective on Dementia and Dementia-Related Psychosis: An Interview With George T. Grossberg, MD

An editor from *The American Journal of Managed Care*[®] spoke with George T. Grossberg, MD, to discuss the unmet needs in dementia-related psychosis and the burden on patient outcomes, caregivers, and the health care system. Grossberg is the Samuel W. Fordyce Professor and director of geriatric psychiatry in the Department of Psychiatry and Behavioral Neuroscience at Saint Louis University School of Medicine in Missouri.

AJMC[®]: Given that population health efforts are driven by data, which include patient and disease identification, how can diagnosis and the associated coding of dementia improve to better identify patients and drive the analytics needed to understand and support these patients?

Grossberg: That is a really good question and a difficult one. From a research perspective, we have asked: Are dementia patients diagnosed early? If not, how late into the disease are they diagnosed? Sometimes, we have found, it can be 3 to 5 years after a person starts to have cognitive or other types of brain-related changes before the family finally brings them to the doctor. Educating caregivers, the lay public, and professional caregivers—whether they are primary care doctors or other health care providers—to ask the right kinds of questions when they see older adults and to suspect the presence of cognitive disorders much earlier will have a tremendous impact. I do not think we are doing enough in that regard.

[The coding arena] is somewhat controversial. We have codes for the various dementias and for dementias with various behavioral abnormalities, but I do not think misdiagnosis is necessarily a code-driven issue. [Often] I think it is a time-driven issue. It is not easy to diagnose dementias. This applies to not only primary care, in particular, but to all doctors and health care providers who are busy and have a packed waiting room. It is not a “12-minute diagnosis.” Diagnosing dementia requires a detailed history from a reliable informant, which is often the family. It may take 2 or 3 visits to the provider to focus on impaired cognition and make the appropriate diagnosis. The development of codes for specific behavioral problems could force health care providers to ask not only about cognitive issues but also issues related to irritability, delusions, firm false beliefs, accusatory behaviors, hallucinations, and anything unusual or untoward in the behavioral arena.

AJMC[®]: Costs are clearly higher in patients with dementia compared with those without. From your perspective, what is driving that utilization? What services and needs are required for these patients?

Grossberg: Data and evidence show that patients with dementia are expensive to our health care economies.¹ The primary reason they are so costly is that if they are living independently and they have cognitive impairment, they are usually not paying attention to their other comorbid medical conditions. For example, if the patient has high blood pressure, diabetes, arthritis, or similar comorbidities, and they are supposed to control their condition with medications they were prescribed, often the medications are not taken or not taken properly.² Because they are unable to properly adhere to the medication regimen their health care provider recommended, they may decompensate from those other comorbid medical problems [and therefore] have more doctor visits, urgent care visits, and hospitalizations. It is important, in those situations, to recognize that patients may need to have a medication monitoring system in place and/or the family needs to be informed. We also know that because behavioral issues are common in patients with dementia, severe behavioral problems may trigger emergency department visits and hospitalizations.^{3,4}

AJMC[®]: Please describe some of the burdens that, aside from costs, are more difficult to measure for patients, caregivers, and their families.

Grossberg: Caregivers of patients with dementia are often older—such as an older spouse taking care of an older adult with dementia—and the behavioral problems of the disease add to their stress and psychological burden, often leading to depression in the caregivers.⁵ These are all contributing factors to cost as well as the psychological burden in this older adult population.

Furthermore, these unpaid caregivers [are often] adult daughters or sons [who] may have to take off from work if their parent is experiencing a problem, [they] have to take [the patient] to the doctor, or [the patient is] decompensating or having behavioral problems. It is a huge impact and a major cost to society, as well.

AJMC[®]: Most of the care for patients with dementia is provided by primary care providers, such as family or general practitioners, internal medicine physicians, and nurse practitioners. How well is that working? What opportunities exist to introduce more specialty care for either direct management or as part of a team-based approach to supporting patients?

Grossberg: For sure, primary care providers are overwhelmed with the boom of the older adult population, particularly the explosive growth in people 80 or 85 years or older who have the highest risk of Alzheimer disease and other dementias.¹ Primary

care providers often don't have the time or expertise to diagnose and manage the problems that are associated with the various dementias. Increased education [about dementia] is necessary, particularly about the importance of including family members, arguably the most reliable informants, [in conversations].

For example, recently I had an encounter with a patient, aged 85 years, and her daughter. The patient is well-kept, articulate, and highly educated. She and her daughter came to see me because the daughter had some concerns related to her mother's memory, cognition, and suspicion of early dementia. When I asked the patient about her memory, she replied, "Oh, my memory is great, doctor. There's nothing wrong with my memory. In fact, I have a better memory than most people my age." Of course, when I spoke with her daughter, I found out that the patient was forgetting things. It is important for primary care providers to always include the family to have that reliable informant, who will sensitize and make our diagnoses much more precise.

AJMC®: Does a model in practice exist that can be replicated?

Grossberg: One model is from the University of Washington in Seattle; its [initial] focus was depression among older adults. The team of investigators embedded a social worker into a big primary care practice; their job was to look for mental, behavioral, or cognitive changes in older adults and bring any changes to the attention of the primary care provider. When looking at depression, more people who needed to receive diagnoses and be treated for depression were recognized than those that were recognized before [the] social worker who was focusing on mental health issues was there.⁶

A similar model, [where] someone like a social worker, a psychologist, a neuropsychologist, or [another specialist] would focus on cognition, prescreening patients, and bringing [potential problems] to the attention of the primary health care providers could have a high payoff.

AJMC®: Increased neuropsychiatric inventory (NPI) scores reflect increased odds for nursing home placement and increased health care costs. How are these scores used in clinical practice? Do opportunities exist for this information to be used in predictive modeling for population-based efforts to identify high-risk patients?

Grossberg: The NPI is among the many different screening tools used to quantify different behaviors⁷; however, [the NPI] is lengthy and time-consuming and [therefore] generally not used in busy primary care settings. Usually, the primary care doctor, [instead], will talk with the family and [ask if] there have been any unusual behaviors or anything [concerning] rather than using a quantifiable tool. There is no doubt that the use of a tool like [the NPI] would identify patients who need more

intervention or who may be at higher risk of potential institutionalization. It is important for primary health care providers to ask questions akin to those included in the NPI: "Have there been any inappropriate, unusual, or behaviors of concern in the patient?" or "Are they seeing or imagining things?" There needs to be a high index of suspicion that some behavioral issues may exist. Providers should aim to get as much information out of the caregiver or family member as they can to see what kind of impact [the behavior] is having and try to intervene early before the caregiver or family member gets burnt out and stressed out or before the patient harms themselves or others. Then it may be time to think about placement.

AJMC®: Can you describe the impact and burden you've seen in practice for patients with dementia who are experiencing hallucinations or other delusions? How do these symptoms affect how they seek and receive care?

Grossberg: In addition to falls, substantial neuropsychiatric symptoms—including delusions, hallucinations, and agitation—are major reasons for caregiver stress and burnout.⁵ Falls are among the top reasons for nursing home placement in the United States, followed by neuropsychiatric symptoms in the context of dementias, which the family can no longer manage.⁸ One of the associated issues related to neuropsychiatric symptoms and family caregivers is the importance of preemptive education for the family, so the family would know how to recognize these symptoms and how to bring them to the attention of their doctor or health care providers, in addition to behavioral and environmental interventions they could utilize at home.

An example of [an intervention] might be [playing] a recording of family photos, a video of [the caregiver] talking to [the patient] about something from the past or their grandkids before leaving the room, and [the patient] can it watch on television. That way [the caregiver] will be with the patient, albeit electronically, and that can make the patient feel more comfortable [and] less like they are being abandoned. That would be 1 example of an intervention, a behavior technique, that can be useful in moderating that kind of [agitated] behavior.

However, many families do not know about these interventions. Once they learn, families can use interventions that might help prevent them from getting overwhelmed and prevent the worst-case scenarios that lead to hospitalization and/or institutionalization of the patient. We want to keep the patient home as long as possible.

AJMC®: Antipsychotics and mood stabilizers are used off-label for dementia-related psychosis. What risk/benefit considerations do practitioners evaluate? Can you speak to the risks and related implications introduced when these treatments, or others with low evidence, are used to treat these patients?

Grossberg: Sometimes pharmacotherapy is indicated. Primarily, antipsychotic medications are being used off-label for the delusions and hallucinations related to dementia. These drugs have potential adverse events, but it doesn't mean that they are not helpful. Right now, we do not have much of a choice. The risk-benefit ratio of using the current atypical antipsychotics for delusions and hallucinations includes considering black box warnings related to increased cerebrovascular events, stroke-like events, cardiovascular events, and even increased mortality. Certainly, these drugs may be considered in urgent and emergency situations; although they are off-label, they may be useful. However, they come with risk. FDA-approved alternatives that are safe and effective need to be developed, particularly for indications like delusions and hallucinations related to dementia.

AJMC®: What key points would you like to share with the managed care audience about dementia-related psychosis?

Grossberg: One key point is that approximately 90% or more of patients with dementia, in the long-term care environment in particular, have neuropsychiatric symptoms such as delusions, hallucinations, agitated behaviors, apathy, and depression.⁹ They are ubiquitous. The percentage is not quite as high in patients who are at home. About 75% of [patients with] Lewy body dementia,¹⁰⁻¹³ 50% of [patients with] Parkinson [disease] dementia,^{10,11,14} and about 30% of [patients with] Alzheimer disease experience psychotic symptoms.^{3,11,12,15-20} If the goal is to keep people out of the long-term care setting, what needs to be increased is education on diagnosing and managing the symptoms of dementia before they get out of control and the caregivers become burned out in the home. Even in the long-term care environment, recognition, management, appropriate treatment, and intervention can go a long way toward helping the patients and the professional caregivers continue to manage these challenging and difficult-to-treat patients. And, of course, safe and effective FDA-approved options for treating dementia-related psychosis are needed. •

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