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MORE THAN COGNITION

Understanding the Impact and Consequences of Hallucinations and Delusions Associated With Dementia-Related Psychosis From the Neurologist, Psychiatrist, and Caregiver Perspectives

An expert panel of neurologists and psychiatrists share their clinical perspectives on the prevalence, impact, and potential consequences of dementia-related hallucinations and delusions, with insights from a caregiver of an adult living with Alzheimer's disease dementia and experiencing hallucinations and delusions.

Prevalence

Dementia is common in older adults in the United States (US), with approximately 7.9 million people living with dementia, of whom 3.95 million carry a diagnosis of at least 1 type of dementia.[1-3]

Neuropsychiatric symptoms—including hallucinations, delusions, agitation/aggression, depression, apathy, euphoria, anxiety, disinhibition, irritability/lability, and aberrant motor behavior (eg, wandering)—are common across the dementias.[4,5] Nearly all people with dementia experience these symptoms. A large proportion (79%) of adults with dementia in long-term care facilities were reported to have at least 1 clinically significant neuropsychiatric symptom (defined as a Neuropsychiatric Inventory [NPI] score ≥4), and 97% of community-dwelling adults with dementia were reported to have at least 1 neuropsychiatric symptom.[4,5]

The onset of these symptoms can occur at various times in the course of illness.[6] Jost et al conducted a retrospective medical chart review of 100 randomly selected patients with autopsy-confirmed Alzheimer's disease to characterize the prevalence and time of onset of psychiatric symptoms.[6] Social withdrawal, suicidal ideation, depression, paranoia, anxiety, diurnal rhythm disturbances, and mood changes occurred early in the course of the disease (before diagnosis), whereas irritability, hallucinations, delusions, agitation and aggression, wandering, and sexually inappropriate behavior were documented within 2 years, on average, after diagnosis.[6]

With regard to dementia-related hallucinations and delusions in particular, approximately 2.4 million people with dementia in the US experience these symptoms; the rates vary based on dementia type **(Table 1)**.[7-21]

Table 1. Prevalence of Hallucinations and Delusions by Dementia Type[7-21]

	No. of People in US With Dementia	Overall Psychosis Prevalence	Hallucinations Prevalence	Delusions Prevalence
Alzheimer's Disease Dementia[7-14]	~5.5 million	30%	11%-17%	10%-39%
Vascular Dementia[7,10,12,14]	~1.6 million	15%	5%-14%	14%-27%
Dementia With Lewy Bodies[10,15-18]	~430,000	75%	55%-78%	40%-57%
Parkinson's Disease Dementia[10,13,17,19]	~320,000	50%	32%-63%	28%-50%
Frontotemporal Dementia[20,21]	~80,000	10%	1.2%-13%	2.3%-6%
		~2.4 million people in the US have dementia-related hallucinations and delusions		

This disease-awareness, non-CME newsletter is intended only for healthcare professionals involved in the management of people with dementia-related hallucinations and delusions and is sponsored by ACADIA Pharmaceuticals Inc. This newsletter is not meant to address specific treatment options for dementia-related psychosis.

Symptom Identification

With these prevalence rates in mind, Gary W. Small, MD, and Marwan Sabbagh, MD, emphasized the importance of identifying hallucinations and delusions in people with dementia. "One reason it's so important to detect hallucinations and delusions is that they could be a manifestation of an underlying medical condition, and you want to find that out right away and deal with it," said Dr. Small. "Therefore," Dr. Sabbagh added, "we as healthcare professionals need to become proficient at identifying these symptoms."

How can clinicians look for and recognize hallucinations and delusions? A hallucination is a perception-like experience that occurs without an external stimulus and is sensory (eg, auditory, visual, olfactory, gustatory, or tactile) in nature.[22] A delusion is a false, fixed belief, despite evidence to the contrary. For example, a patient may be convinced that a spouse is being unfaithful or that a family member is stealing from him or her.[22]

To better understand the frequency and phenomenology of these symptoms in people with dementia, Ballard et al studied 124 people aged 65 years or older diagnosed with mild or moderate dementia of any type.[15] Most frequently reported (21% to 22%) were delusions of reference, theft or possessions being hidden, and strangers in the house.[15] Second-person auditory hallucinations, visual hallucinations of animals or insects, and visual hallucinations of relatives in the house were reported at a frequency of 8.1% to 20.2%.[15]

To fill a need for specific diagnostic criteria for psychosis in dementia, Jeste and Finkel proposed a set of criteria **(Figure 1)** intended to distinguish symptoms of psychosis with Alzheimer's disease from those seen with delirium (although they can coexist for a time); other medical conditions; substance use; and primary psychiatric conditions, such as schizophrenia, delusional disorder, and mood disorder with psychotic features.[23] These criteria may also apply to psychosis associated with other dementia types, but more research is needed.[23]

Figure 1. Proposed Diagnostic Criteria of Psychosis in Alzheimer's Disease[23]

A Characteristic symptoms	**B** Primary diagnosis	**C** Chronology of symptoms onset	**D** Duration and severity
Presence of 1 or more of the following symptoms: • Visual or auditory hallucinations • Delusions	All criteria for dementia of the Alzheimer's type are met*	Evidence from patient history indicates that the symptoms defined in Criterion A have not been present continuously since prior to the onset of dementia symptoms	Symptoms defined in Criterion A have been present at least intermittently for 1 month or longer, and are severe enough to cause disruption in patients' and/or others' functioning
E Exclusion of schizophrenia and related psychotic disorders	**F** Relationship to delirium	**G** Exclusion of other causes of psychotic symptoms	**H** Associated features
Criteria for schizophrenia, schizoaffective disorder, or mood disorder with psychotic features have never been met	The disturbance does not occur exclusively during the course of a delirium	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)	Specify if disturbance is associated with: • Agitation • Negative symptoms • Depression

***For other dementias, such as vascular dementia, Criterion B will need to be modified appropriately.**

EXPERT PERSPECTIVE

Prevalence of dementia-related hallucinations and delusions
What are the implications for clinical practice?

Psychiatrist perspective:
"Delusions are fairly common in Alzheimer's disease: Maybe 1 in 5 patients do develop delusions. Hallucinations as an initial symptom occur more commonly in Lewy body dementia."—Dr. Devanand

Neurologist perspective:
"I think people pay attention to cognition in the milder stage. But once the emergence of the neuropsychiatric features take place, that overwhelms the situation, and they stop even paying attention to the cognitive issues. So it's a huge and worrisome and important milestone in the disease."—Dr. Sabbagh

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EXPERT PERSPECTIVE

Confirming dementia-related hallucinations and delusions
What is your experience in clinical practice?

Psychiatrist perspective:
"A medical evaluation is necessary for patients with hallucinations and delusions. You want to be diligent, because treating that medical condition could sometimes treat the hallucination or delusion."—Dr. Small

Neurologist perspective:
"Before you just say [that] this is part of the progression, you've got to check it out. I would scan them; I would take a urine sample; I would do blood work; and I would check their medication list. We still are doctors, and we have to be medical in our approach first before we default to the dementia." —Dr. Sabbagh

Proposed Neurobiology

The neurobiology of psychosis, particularly its expression in the context of dementia, is complex and unknown. Researchers have conducted various imaging studies to determine the underlying neurobiology of hallucinations and delusions in dementia-related psychosis, and Jeffrey Cummings, MD, ScD, noted that this structural and functional neuroimaging implicates the frontotemporal regions. Dr. Small added, "We know that often the frontal lobe of the brain shows lower glucose metabolism in these patients. That makes sense because the frontal lobe is the thinking brain; it is the executive branch of the brain, and so the filter is gone as a result."

Mega et al used single-photon emission computed tomography, or SPECT, to identify the functional neuroimaging correlates of symptoms of psychosis in people with Alzheimer's disease.[24] The study found that the group with symptoms of psychosis (n=10, all of whom had delusions and half of whom had hallucinations) showed significantly lower perfusion in the left and right prefrontal areas, left striatum, and left parietal cortex (P<0.0001) than the group without symptoms of psychosis (n=10).[24]

Similarly, Nagahama et al combined 17 symptoms of psychosis associated with dementia with Lewy bodies into 5 symptom domains using factor analysis and examined the relationships between regional cerebral blood flow and the presence of each symptom domain in individuals with dementia with Lewy bodies (N=100).[25] The significant hypoperfusion areas in patients with dementia with Lewy bodies relative to controls involved a wide range of bilateral frontal, temporal, parietal, and occipital cortices.[25] Of the 100 patients, 74 patients with visual hallucinations showed significant hypoperfusion in the left angular gyrus, left occipital gyrus, right supramarginal gyrus, and right angular gyrus compared to those without visual hallucinations (P<0.001).[25]

Also of note, grey-matter loss has been identified in Parkinson's disease with visual hallucinations. Ibarretxe-Bilbao et al compared progressive grey-matter loss in people with Parkinson's disease with (n=12) or without (n=14) visual hallucinations to healthy controls (n=12).[26] At follow-up, 75% of patients with visual hallucinations had developed dementia.[26] The individuals with visual hallucinations also showed more extensive grey-matter loss, involving limbic, paralimbic, and neocortical areas, compared with those without visual hallucinations, who showed deterioration only in small clusters of frontal areas and the cerebellum (P<0.05).[26]

Researchers have also explored the proposed role of neurotransmitters in the neurobiology of psychosis. Historically, the neurotransmitter dopamine was implicated in psychosis, but additional research has suggested that 3 neurotransmitter systems are thought to be involved: dopamine, glutamate, and serotonin.[27,28] These 3 neurotransmitter pathways appear to interact in a proposed cortico-limbic pathway of psychosis.[27,28] In the cortex, cortical glutamatergic neurons have serotonin 2A (5-HT_{2A}) receptors, and their activity is modulated by serotonin arriving via projections from the Raphe nucleus. Increased signaling via these 5-HT_{2A} receptors can drive aberrant cortical activity and is proposed to be linked to visual hallucinations.[29-33]

In addition to the serotonergic mechanism, cortical glutamatergic neurons can also be aberrantly activated by hypofunction of N-methyl-D-aspartate (NMDA) receptors on cortical inhibitory neurons. NMDA receptor hypofunction has been shown in vitro to reduce inhibitory tone in the cortex and is thought to cause glutamatergic neurons to be hyperactivated.[34] NMDA receptor hypofunction has been linked to the induction or worsening of psychotic symptoms.[34-37]

In turn, glutamatergic projections from the prefrontal cortex provide tonic control of dopaminergic neurons in the ventral tegmental area (VTA).[38,39] The dopaminergic neurons in the VTA form the origin of the mesolimbic pathway that projects to the ventral striatum.[38-40] Hyperactivity of the dopaminergic mesolimbic pathway has been linked to hallucinations and delusions.[40,41]

To summarize, the dopamine, glutamate, and serotonin pathways appear to be interconnected. Therefore, it is possible that neuropsychiatric symptoms in people with dementia are the result of dysfunction in 1 or more of these neurotransmitter pathways.

Impact on Patients

The presence of hallucinations and delusions may be associated with worse outcomes in people with dementia-related psychosis. To investigate the relationship, Scarmeas et al followed 456 individuals with early Alzheimer's disease at 5 university-based Alzheimer's disease centers in the US and Europe for up to 14 years (mean, 4.5 years).[42] Hallucinations were present in 7% of patients at initial visit and in 33% at any subsequent visit.[42] Delusions were noted for 34% of patients at baseline and for 70% at any subsequent evaluation.[42]

The study assessed the association between the presence of hallucinations and delusions and 4 outcomes: cognitive endpoint, functional endpoint, institutionalization, and death.[42] Cognition was assessed with the Columbia Mini-Mental State Examination (MMSE), and function was assessed with the Blessed Dementia Rating Scale (BDRS) parts I and II.[42] In Cox adjusted models that controlled for cohort, recruitment center, age, sex, education, baseline Columbia MMSE, baseline BDRS, comorbidity index, informant status, behavioral symptoms, and use of cholinesterase inhibitors and neuroleptics, the presence of hallucinations and delusions was associated with a significantly increased risk of cognitive decline (risk ratios: hallucinations, 1.62; delusions, 1.5) and functional decline (risk ratios: hallucinations, 2.25; delusions, 1.41).[42] Further, hallucinations, but not delusions, were associated with a significant increase in the risk of institutionalization (risk ratio, 1.60) and death (risk ratio, 1.49).[42]

Hallucinations and delusions in dementia-related psychosis are quite disruptive to patients' daily lives, concluded Davangere P. Devanand, MD. "We've seen that [this disruption is] really something that takes place throughout the day and night, and you just never know when something is needed," he said. "We have seen that this [can] occur at any stage of dementia."

Caregivers know firsthand the disruptive effects of patients' dementia-related hallucinations and delusions. Linda Gregory, the primary caregiver of her mother, who is living with Alzheimer's disease dementia and related hallucinations and delusions, shared her experience. She described how her mother would wander around her sister's house at night, putting herself at risk for harm. "They had to put on door chimes so that they would know she was going out," said Ms. Gregory. "[My sister] couldn't leave [my mother] in her own room by herself."

Dementia-Related Hallucinations and Delusions and Aggression: Evaluating a Complex Relationship

Hallucinations and delusions in dementia-related psychosis may be associated with aggression. In people with dementia, the association between symptoms of hallucinations and delusions and episodes of aggression is complex. Some studies have found that hallucinations (albeit to a lesser degree) and delusions may be associated with aggression in Alzheimer's disease dementia.

In a study of outpatients with probable Alzheimer's disease by Gilley et al, 270 people were followed for 12 months to examine the relationship between symptoms of hallucinations and delusions and subsequent physical aggression.[1] At baseline, hallucinations were reported in 99 participants and delusions in 128 participants.[1] Hallucinations did not increase the relative risk of physical aggression in this study (relative risk [RR], 1.2; 95% CI, 0.3-2.7; *P*=0.653).[1] However, the presence of delusions increased the relative risk of physical aggression 2.8-fold after controlling for dementia severity and previous episodes of aggression (RR, 2.8; 95% CI, 1.3-4.3; *P*=0.009).[1]

In another cross-sectional study, Leroi et al examined the relationship between psychiatric syndromes and dementia severity in 1155 people diagnosed with probable Alzheimer's disease.[2] Individuals were assessed using the Consortium to Establish a Registry for Alzheimer's Disease, or CERAD; Behavioral Rating Scale; Hamilton Depression Rating Scale, or HDRS; and Blessed Dementia Rating Scale, or BDRS; and symptoms were recorded as either present or absent.[2] In moderate or severe stages of Alzheimer's disease, hallucinations and delusions were associated with an increased odds of aggression (moderate Alzheimer's disease: odds ratio [OR], 2.35; 95% CI, 1.78-3.06; severe Alzheimer's disease: OR, 11.1; 95% CI, 8.4-14.4).[2]

Leonard et al sought to identify modifiable characteristics, including hallucinations and delusions, associated with physical or verbal aggression in nursing home residents at least 60 years of age with dementia.[3] Of the 103,344 residents from 5 states in this cross-sectional study, 7120 (6.9%) were reported to have been aggressive in the week prior to their annual comprehensive health assessment.[3] The presence of hallucinations and delusions significantly increased the odds of physical aggression after adjusting for potential confounders (eg, age, gender, severity of cognitive impairment).[3] Hallucinations were associated with a 1.4-fold increased odds (OR, 1.4; 99% CI, 1.1-1.8), and delusions were associated with a 2.0-fold increased odds (OR, 2.0; 99% CI, 1.7-2.4).[3] Depression was associated with the highest odds of physical aggression in this study (OR, 3.3; 99% CI, 3.0-3.6).[3]

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EXPERT PERSPECTIVE

Hallucinations, delusions, and other neuropsychiatric symptoms in dementia
In your experience, what is the relationship, if any?

Psychiatrist perspective:
"Psychotic experiences [can make someone] aggressive, and that can be scary. It poses a danger for caregivers and patients and the entire [long-term care] staff."—Dr. Small

Neurologist perspective:
"These neuropsychiatric features don't always occur by themselves. They're not occurring in isolation; they come as a cluster."—Dr. Sabbagh

Caregiver Burden

The majority of older adults with dementia receive support from family caregivers.[43] The 2015 National Health and Aging Trends Study and its companion study, the National Study of Caregiving, included 2204 caregivers of 2417 people with dementia aged 65 years or older who lived in community settings and received help with self-care, mobility, or household activities.[43] To put into context the prevalence of informal caregiving for older adults with dementia, approximately 70% received care from family caregivers—ie, their spouse or children.[43]

Moreover, many delusions target the caregiver: "You're stealing my things! You're going to abandon me! You're not my spouse! You're an imposter! You're having an affair!"[15] Ms. Gregory can attest to this reality. "Initially [my mother] was very concerned that my sisters and I were in collusion against her," Ms. Gregory described. "Then she told me 'You just want my money; you just want my house.' She definitely thought I was stealing her things, which was really hard for me to balance, because there *were* things I was taking from her house. She had firearms. I obviously had to take those."

"Caregiving is not an easy job," commented Dr. Small. "We know there's an increased risk for depression. It's like working 3 or 4 jobs at the same time. And [dementia-related hallucinations and delusions] only make matters much worse."

Unmet Need

The complexity of hallucinations and delusions associated with dementia-related psychosis contributes to the ongoing unmet need in the management of these symptoms. "While some progress has been made, we don't have established guidelines, so we are doing the best we can," said Dr. Small. "[Clinicians will] look at the patient's presentation and choose a medication based on the perceived symptoms. However, we don't have [US Food and Drug Administration (FDA)-approved] medicines right now targeted toward these symptoms specifically, so I would say there's a tremendous unmet need for appropriate medicines."

"Yet, families feel an immediacy of need," said Dr. Sabbagh. "They don't want a treatment that's going to work sometime in the future. They want something that's going to work as soon as possible."

Agreeing with Drs. Small and Sabbagh, Dr. Devanand added that there are shortcomings in behavioral interventions as well. "I'm not aware that there's a proper well-studied behavioral approach to handling psychosis," he said. "We have talked about how you do it on a case-by-case basis, but it is difficult to study systematically."

As Dr. Small noted, no antipsychotic medications are currently FDA approved for the treatment of dementia-related psychosis, and all antipsychotics carry a Boxed Warning indicating that

CATIE-AD: Evaluating the Use of Atypical Antipsychotics for Symptoms Associated With Dementia-Related Psychosis

The double-blind, placebo-controlled Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease, or CATIE-AD, study was conducted between 2001 and 2004 at 45 US sites and consisted of 2 phases. In Phase 1, 421 outpatients (mean age, 77.9 years) were randomly assigned double-blind to 1 of 3 atypical antipsychotics or placebo in a 2:2:2:3 ratio. The dose of the antipsychotics could be adjusted as clinically indicated by the study physicians. Treatment could be discontinued after the first 2 weeks if the response was inadequate, while patients with an adequate response could be treated for up to 36 weeks.

Patients whose initial treatment was discontinued (n=253) could be enrolled in Phase 2 of the study. These patients were randomly assigned under double-blind conditions to receive 1 of the antipsychotic drugs to which they were not initially assigned or to receive a selective serotonin reuptake inhibitor.

The primary outcome measure was time until discontinuation of treatment for any reason. The main secondary outcome was the attainment of minimal or greater improvement in the Clinical Global Impression of Change scale at Week 12 while the patients continued to receive the Phase 1 drug.

Reference:
Schneider LS, et al. Effectiveness of atypical antipsychotic drugs in patient with Alzheimer's disease. *N Engl J Med.* 2006;355(15):1525-1538.

elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.[44] The Boxed Warning resulted from an FDA analysis of 17 placebo-controlled trials that demonstrated an approximate 1.6- to 1.7-fold increase in mortality with the use of atypical antipsychotics in older patients with dementia-related psychosis compared to placebo-treated patients.[44] Most deaths were due to either cardiovascular events (eg, heart failure, sudden death) or infections (mostly pneumonia).[44]

Additionally, the Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease (CATIE-AD) evaluated the effectiveness and safety of atypical antipsychotics in 421 patients with Alzheimer's disease and hallucinations, delusions, aggression, or agitation (see sidebar on previous page for study details).[45]

Phase 1 of the CATIE-AD study found no significant overall differences among treatment groups in time to discontinuation for any reason.[45] It also reported no significant differences in response rate at 12 weeks.[45] The overall rate of discontinuation for any reason at 12 weeks was 63%.[45] Further, discontinuation of treatment due to intolerability of the study drug, adverse events, or death ranged from 16% to 24%, depending on the atypical antipsychotic, and was 5% with placebo (P=0.009 for Kaplan-Meier estimate of time to discontinuation, overall comparison).[45]

There were no significant differences among the groups with regard to the proportion of patients who had at least 1 serious adverse event and the proportion who had any adverse event.[45] In Phase 1, the rate of individual adverse events also was examined.[45] The following adverse events were reported more commonly with atypical antipsychotics than placebo, and the differences among the treatment groups were statistically significant: sedation, cognitive disturbance, psychotic symptoms, and confusion or mental-status change.[45] In the same study, patients who received atypical antipsychotics also experienced higher rates of extrapyramidal symptoms or parkinsonism (2%-12%, depending on the atypical antipsychotic) than patients who received placebo (1%) (P<0.001).[45]

By design, the CATIE-AD study included measures at baseline and during follow-up to assess the effects of time and treatment on cognitive function.[46] Vigen et al analyzed these outcomes among 357 patients (mean age, 77.6 years) for whom baseline measures and at least 1 follow-up assessment during the 36-week observation period were available.[46] These measures included the MMSE; the cognitive factor on the Brief Psychiatric Rating Scale (BPRS); Alzheimer's Disease Assessment Scale (ADAS) subscales of cognition, concentration/distractibility, number cancellation, and executive function (mazes); category instances tests; finger-tapping tests (preferred and nonpreferred hands); Trail Making Test Part A; and working memory deficit.[46] The researchers also calculated a cognitive summary score by averaging the normalized z scores for each of the component measures (ADAS subscales, category instances tests, finger-tapping tests, Trail Making Test Part A, and working memory deficit) and then normalizing these averaged scores.[46]

Significant worsening of cognitive function from baseline was reported for MMSE (P=0.004), BPRS cognitive factor (P=0.05), category instances tests (P=0.01), and cognitive summary score (P=0.004).[46] A significant difference from baseline was not observed for the ADAS subscales, finger-tapping tests, Trail Making Test Part A, and working memory deficit.[46]

Conclusions

Dementia involves more than a deterioration in cognitive function. Neuropsychiatric symptoms, such as hallucinations and delusions, are prevalent across the dementias and can occur at various times in the course of the illness.

While the neurobiology of dementia-related hallucinations and delusions is complex and unknown, research suggests that hallucinations and delusions in dementia-related psychosis are not solely triggered by increases in brain dopamine. It is proposed that glutamate and serotonin also play important roles, in particular to decreases in serotonergic neurotransmission. Growing evidence further shows that neuroanatomic changes may be a factor.

The presence of hallucinations and/or delusions may be associated with an increased risk of cognitive and functional decline, institutionalization, and death among patients with dementia. The majority of these patients require support from family caregivers, though caregivers are often the target of delusions.

Ms. Gregory takes a day-by-day approach to her mother's care and has sought structure and guidance from healthcare professionals. "I didn't really know what I was anticipating when [my mother] got this Alzheimer's diagnosis," she said. "I'm really grateful … that there are people out there who truly care about the caregivers, the families, and the patients."

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EXPERT PERSPECTIVE

Managing hallucinations and delusions
What are your views on symptom management?

Psychiatrist perspective:
"I like the approach of education. It's important to try to help caregivers understand what's going on and what the behaviors are."—Dr. Small

Neurologist perspective:
"Treatment is beyond a single medication. It starts with a very involved conversation, and there's no easy solution. There's no one *solution; there's no one-size-fits-all."—Dr. Sabbagh*

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