# Managing the Burden of Dementia-Related Delusions and Hallucinations

Gary W Small, MD

## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

- Identify the burden experienced by patients with dementia-related delusions and hallucinations.
- Assess patients with dementia for the presence of delusions and hallucinations.
- Individualize treatment in patients with dementia-related delusions and hallucinations.
- Align treatment of patients with Parkinson's psychosis with current recommendations.

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of dementia-related delusions and hallucinations.

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## INTRODUCTION

Dementia is defined as a clinical syndrome that involves a cognitive impairment severe enough to impair the patient's ability to function independently.[1] Many different conditions can cause dementia, which is often characterized by a decline in memory, language, problem-solving, or other thinking skills. The most common form of dementia, occurring in up to 70% of the estimated 8 million people living with dementia in the United States, is Alzheimer's disease (AD).[2] Other subtypes include vascular dementia (20%), dementia with Lewy bodies (5%), Parkinson's disease (PD) dementia (4%), and frontotemporal dementia (1%).[2-4] Many patients with dementia have several different causes, eg, combined vascular dementia and AD.[5] Although dementia may occur in younger adults, the prevalence of dementia increases with age, affecting 2% of those age 65 to 69 years and 33% pf those age ≥90 years.[6] Due to the aging US population, the prevalence of dementia is expected to grow, with some estimates indicating a tripling of AD dementia prevalence by 2050.[7]

Neuropsychiatric symptoms are commonly experienced by people with dementia.[8] Symptoms that typically occur earlier in the course of dementia, often before diagnosis, include social withdrawal, suicidal ideation, depression, paranoia, anxiety, diurnal rhythm disturbances, and/or mood changes.[9] Symptoms that generally first appear shortly after diagnosis include irritability, delusions and hallucinations, agitation and aggression, wandering, and/or sexually inappropriate behavior.[9]

Delusions and hallucinations are among the signs and symptoms associated with a loss of contact with reality, or psychosis. A delusion is a false, fixed belief despite evidence to the contrary, whereas a hallucination is a perception-like experience that occurs without an external stimulus and is sensory in nature.[10] An estimated 2.4 million people in the United States have dementia-related delusions and hallucinations.[11,12] The prevalence of delusions and hallucinations vary based on the type of dementia. They are most common in patients with dementia with Lewy bodies or PD, occurring in 75% and 50%, respectively, and least common in patients with AD or vascular dementia (<30%).[11,12] Older adults with dementia may experience delusions and/or hallucinations 2 to 6 times per week.[13] Delusions persist longer than 3 months in 82% of patients with dementia and hallucinations in 52%.[14,15]

## BURDEN OF DEMENTIA-RELATED DELUSIONS AND HALLUCINATIONS

### Patient burden

Dementia-related delusions and hallucinations contribute to a wide variety of behavioral and psychological symptoms. These symptoms include insomnia, confusion, agitation, personality change, self-care problems, and cognitive and functional impairment.[16] Dementia-related delusions are associated with a 2- to nearly 3-fold increased risk of aggression, and dementia-related hallucinations with up to a 1.4-fold increased risk of aggression.[17,18] A prospective analysis of patients with early-stage AD (N=456) at baseline followed for 14 years showed that delusions were associated with an increased risk of cognitive (relative risk [RR] 1.50; 95% confidence interval [CI], 1.07-2.08) and functional (RR 1.41; 95% CI, 1.02-1.94) decline.[19] The effect of AD-related hallucinations is even greater, as the analysis showed greater risk of cognitive (RR 2.25; 95% CI, 1.54-2.27) and functional (RR 2.25; 95% CI, 1.13-2.28) decline. Moreover, patients who experienced hallucinations were at increased risk for institutionalization (RR 1.60; 95% CI, 1.13-2.28) and death (RR 1.49; 95% CI, 1.03-2.14).

By contrast, a case-control study that examined the association between the Neuropsychiatric Inventory (NPI) score in older adults with AD (N=641) showed no increased risk of nursing home placement in persons with dementia-related hallucinations.[20] However, persons with AD and agitation/aggression, disinhibition, irritability, delusions, sleep disorder, or appetite disorder were significantly more likely to be placed in a nursing home. Overall, a 10% increase in the total NPI score was associated with a 30% increased odds of nursing home placement.

A population-based study of older adults with possible or probable AD dementia indicated that those with dementia-related psychosis were twice as likely to progress to severe dementia and 1.5 times more likely to die during the 3 to 5 years of follow-up.[21] The presence of psychosis appears to portend a more severe disease course, particularly for patients with both delusions and hallucinations compared with patients with only delusions or hallucinations.[22]

The occurrence of delusions also appears to be associated with a severe disease course compared to people with dementia who do not experience delusions. A 2-year longitudinal analysis of older adults with AD showed that a delusion of theft was related to the degree of cognitive dysfunction and functional impairment, while a delusion of abandonment was related to the severity of cognitive impairment.[23] By contrast, hallucinations were not associated with the degree of cognitive or functional impairment.

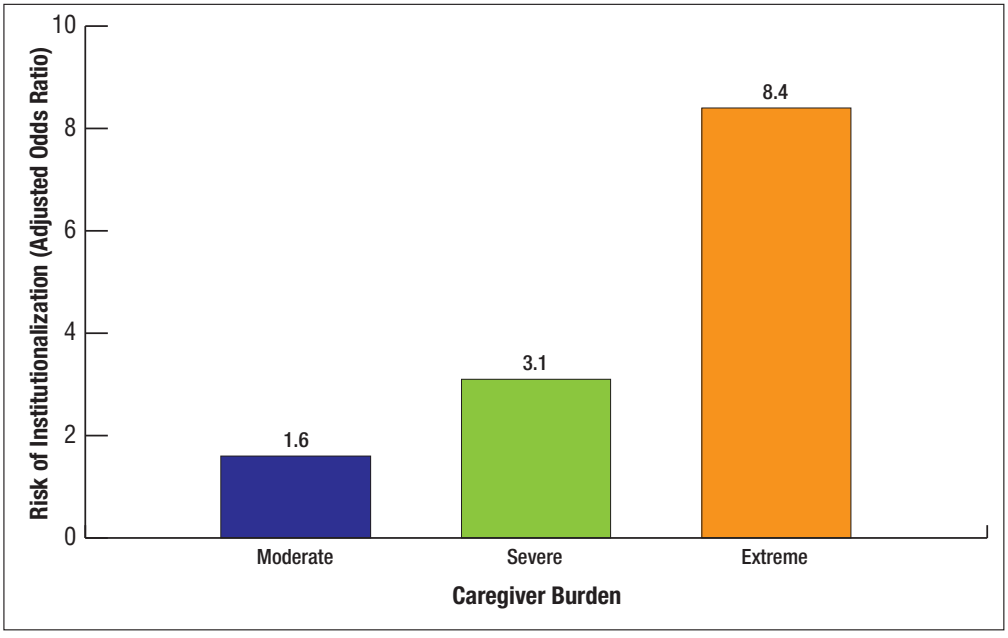
For patients with dementia, the occurrence of delusions appears to be associated with a severe disease course compared to people with dementia who do not experience delusions.

### Caregiver burden

The burden of psychosis-related dementia extends beyond patients to their caregivers.[24] Because two-thirds (64%) of older adults with dementia require assistance with ≥2 self-care or mobility activities and 70% of older adults with dementia receive help from family caregivers, the patient's family is particularly affected.[6] Delusions, irritability, and agitation/aggression in people with dementia are among the most distressing neuropsychiatric symptoms for family caregivers.[25] Common delusions that target the caregiver relate to accusations of theft, abandonment, and spousal infidelity.[13,26] The stress experienced by caregivers – family as well as professional – can even impair their memory abilities.[27] Behavioral problems in older adults with dementia often lead to caregiver depression and a greater sense of burden.[28]

Heightened caregiver burden is a major reason for earlier institutionalization of the individual with dementia.[26,29]

FIGURE 1. **Association of caregiver burden with risk of institutionalization of patients with dementia[26]**




One investigation showed that, over a 5-year period, patients with dementia were more likely to be institutionalized when their caregivers reported moderate, severe, or extreme burden by a factor of 1.6, 3.1, and 8.4, respectively (**FIGURE 1**).[26] Professional caregivers in long-term care facilities also report high levels of emotional exhaustion and burnout, particularly when caring for residents with agitated behavior.[29]

## DIAGNOSTIC CRITERIA OF DEMENTIA-RELATED PSYCHOSIS

Diagnostic criteria for psychosis have been proposed for patients with dementia due to AD and related dementias.[30] Key criteria include requiring that patients must have had visual or auditory hallucinations and/or delusions for a month or more, but those symptoms of psychosis must not have been present continuously prior to the onset of dementia symptoms. The onset of the hallucinations and/or delusions is generally insidious rather than acute as might be observed with delirium secondary to underlying dehydration, urinary tract infection, or acute pain syndrome.[31] The hallucinations and/or delusions must be severe enough to cause some disruption in functioning of the patient and/or others.[30] Psychotic symptoms often occur with associated features, such as agitation, apathy, or depression.[30]

As implied by these proposed criteria, a key initial objective in assessing the patient with dementia who exhibits psychotic symptoms is to identify any underlying medical condition or risk factor for psychosis, such as chronic bed rest, sensory impairment, or social isolation.[31] Psychosis that occurs for the first time in late life is likely due to dementia or some neurologic condition such as PD or stroke. Psychosis that occurs earlier in life is more likely due to schizophrenia, mood disorder, or some other primary cause.[31] For confirmation that dementia is the cause of the psychosis, it is also necessary to determine that the psychotic symptom does not occur exclusively during the course of a delirium.[30] Consideration also should be given to a substance of abuse as a reason for the symptoms, or an iatrogenic cause such as medications. For example, dopaminergic and anticholinergic medications are common causes of psychosis in patients with PD.[32]

## TREATMENT OF DEMENTIA-RELATED PSYCHOSIS

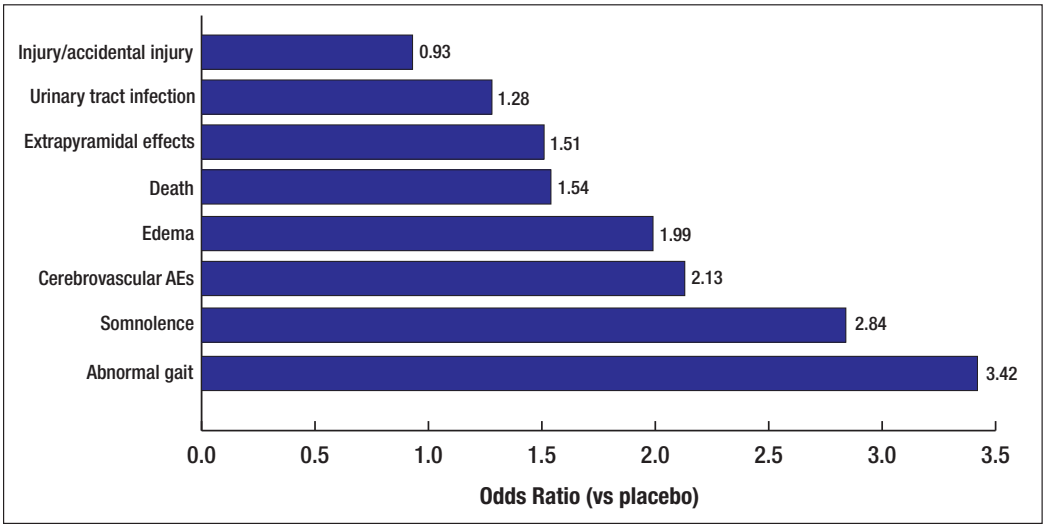
The treatment of psychosis in patients with dementia is multifaceted and is guided by the findings from the diagnostic evaluation. In addition to treating the symptoms of dementia, symptoms caused by underlying medical conditions, medications, or environmental and psychosocial triggers are important targets.

### Nonpharmacological treatment

The Alzheimer's Association and the American Psychiatric Association recommend nonpharmacological approaches as first-line therapy for nonemergency dementia-related psychosis.[33,34] The use of nonpharmacological approaches is reasonable as an initial intervention unless the patient's psychotic symptoms pose a high safety risk to themselves or others, in which case hospitalization is appropriate. Nonpharmacological approaches typically focus on the caregiver strategies and the environment in which care is provided, because patient and caregiver burden is so strongly linked to the likelihood of patient institutionalization.[34] Consequently, caregiver distress is important to identify and address.

Caregivers should be educated to provide a variety of psychosocial interventions that might be helpful to the patient. These interventions include[33,34]:

FIGURE 2. **Adverse events associated with atypical antipsychotics in patients with dementia**[39]




**Abbreviations:** AE, adverse event.
**Note:** The odds ratio for all events (except injury/accidental injury) is statistically significant compared to placebo.

- Providing routine activities, including exercise
- Providing cues to heighten orientation
- Maintaining a calm environment by reducing environmental clutter and ambient noise, optimizing lighting and walkways, and playing music
- Separating the patient from environmental triggers of symptoms, eg, background noises
- Avoiding responses that contradict the patient's perception of reality and respecting their ideas about and explanation for their perceptions, even if incorrect
- Speaking slowly and calmly in a normal tone of voice
- Redirecting the person to participate in an enjoyable activity or offering comfort food or comforting comments

Caregiver resources are available through the Alzheimer's Association (www.alz.org) and Parkinson's Foundation (https://www.parkinson.org/Living-with-Parkinsons/For-Caregivers).

## Pharmacological treatment

### *Antipsychotics*

Antipsychotic therapy plays a central role in the treatment of psychosis, but the US Food and Drug Administration (FDA) has not approved a pharmacological treatment for dementia-related psychosis. Nonetheless, off-label use of atypical, or second-generation, antipsychotics has been the mainstay of pharmacological treatment for psychotic symptoms and agitation in patients with dementia. Antipsychotics are most effective for improving positive psychotic symptoms, eg, delusions and hallucinations, with less benefit for negative symptoms, eg, flat affect.

The use of antipsychotics for dementia-related psychotic symptoms is not without risk. A 2005 FDA analysis concluded that the use of atypical antipsychotics is associated with increased mortality in older adults with dementia.[35] Subsequent investigations confirmed these findings and extended the increased mortality risk to include conventional, ie, first-generation, antipsychotics.[36-38] Moreover, in patients with dementia, atypical antipsychotics have been shown to be associated with cognitive decline and increased risk of metabolic events such as glycemic abnormalities and elevated lipids, as well as an increased risk of adverse events, including abnormal gait, somnolence, edema, extrapyramidal symptoms, and urinary tract infections (**FIGURE 2**).[38-40]

Consequently, most antipsychotics are not approved for the treatment of psychotic symptoms in patients with dementia. In addition, all antipsychotics carry a black box warning indicating that elderly adults with dementia-related psychosis treated with antipsychotic medications are at an increased risk of death.

The FDA analysis and subsequent investigations led the American Geriatrics Society to recommend against the use of conventional and atypical antipsychotics in older adults, particularly those with dementia, as described in their updated "2019 Beers criteria for potentially inappropriate medication use in older adults."[41] In fact, the Beers criteria recommend avoiding the use of all antipsychotics (except quetiapine, clozapine, and pimavanserin) in older adults with PD, as their use may worsen parkinsonian symptoms.

Nonemergency use of antipsychotics may, however, be considered for patients with behavioral problems of dementia or delirium, if such patients have not achieved an adequate response to nonpharmacological therapy and pose a risk to themselves or others, or when the symptoms are of significant distress to the patient.[34,41] A decision to use antipsychotics in such situations should be based on a discussion of the potential risks and benefits from antipsychotic

medication with the patient, family, or others involved with the patient. Antipsychotic treatment should be initiated at a low dose and titrated to the minimum effective dose as tolerated.[34]

### *Pimavanserin*

While no medications have been approved by the FDA for dementia-related psychosis, one atypical antipsychotic, pimavanserin, may be useful in these patients. Pimavanserin has a unique pharmacological profile that acts through a combination of inverse agonist and antagonist activity at serotonin type 2A receptors and, to a lesser degree, serotonin type 2C receptors. This is in contrast to atypical antipsychotics that are thought to exert their effects largely through antagonism of the dopamine type 2 and serotonin type 2A receptors. Pimavanserin is approved for the treatment of hallucinations and delusions associated with PD psychosis.

The approval of pimavanserin was based on a double-blind, placebo-controlled study of 199 patients with PD age ≥40 years. Patients could not have been diagnosed with dementia concurrent with or before PD.[42] After a 2-week lead-in phase to limit the placebo response, patients were randomized to pimavanserin 40 mg/d or placebo. Improvement of the primary outcome, as assessed using the Scale for Assessment of Positive Symptoms adapted for PD (SAPS-PD), was significantly greater with pimavanserin compared with placebo. From a baseline score of 15.9, the SAPS-PD score for patients given pimavanserin decreased to 10.1 after 6 weeks of treatment, while treatment with placebo led to a decrease from a baseline score of 14.7 to 12.0 ($P$=.001). Significant improvement with pimavanserin was also observed with respect to separate measures of hallucinations and delusions. Treatment-emergent adverse events occurring in ≥5% in either group (pimavanserin vs placebo) included urinary tract infection (13% vs 12%), falls (11% vs 9%), hallucinations (7% vs 4%), peripheral edema (7% vs 3%), nausea (6% vs 6%), confusion (6% vs 3%), and headache (1% vs 5%). There was no evidence of treatment-related impairment of motor function in either group. Ten patients in the pimavanserin group (6 because of psychosis) and 2 patients in the placebo group discontinued because of an adverse event.

The safety and efficacy of pimavanserin also have been investigated in a phase 2 trial involving 181 nursing home patients with possible or probable AD and psychotic symptoms.[43] Following 6 weeks of treatment, significantly greater improvement in the NPI-Nursing Home version was observed in patients treated with pimavanserin vs placebo.[43] No adverse effect on cognition or motor function was observed; more patients treated with pimavanserin experienced agitation.

The phase 2 SERENE (NCT02992132) and phase 3 HARMONY (NCT03325556) trials have evaluated the safety and efficacy of pimavanserin in patients with psychosis and either AD or various common subtypes of dementia, respectively. The extension phase of SERENE was completed in February 2019, but no data have been published. HARMONY was recently stopped early after the planned interim efficacy analysis showed pimavanserin to demonstrate a significantly longer time to relapse of psychosis compared with placebo.

## SUMMARY

Neuropsychiatric symptoms such as delusions and hallucinations are commonly experienced by the estimated 8 million persons with dementia in the United States. Dementia-related delusions and hallucinations result in a wide variety of behavioral and psychological symptoms that contribute to substantial patient and caregiver burden and portend a more severe disease course of dementia. The diagnosis of dementia-related psychosis is based on clinical findings, with a key objective to rule out medical and other causes of the psychosis. Nonpharmacological approaches are generally first-line treatment, except when urgent symptom control is needed. None of the antipsychotics currently available are approved for dementia-related psychosis; in fact, antipsychotics are associated with increased mortality in older adults with dementia. Pimavanserin is an atypical antipsychotic with a unique mechanism of action that is approved for the treatment of hallucinations and delusions associated with PD psychosis; some evidence indicates the safety and effectiveness of pimavanserin for patients with dementia-related psychosis. ●

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