



# Combating Agitation in Alzheimer's Dementia:

## Real-World Approaches



Agitation in Alzheimer's dementia worsens the impact of an already devastating and burdensome disease.<sup>1,2</sup> It is associated with substantial patient burden and long-term consequences.<sup>3,4</sup> The International Psychogeriatric Association (IPA) groups behaviors of agitation in cognitive disorders as excessive motor activity, verbal aggression, or physical aggression.<sup>5</sup>



Caregiver-targeted interventions and partnership between healthcare practitioners and caregivers can improve patient outcomes.<sup>6</sup> Interventions for family caregivers, such as skills training, caregiver education, and collaborative care with healthcare practitioners, have the potential to reduce the frequency and severity of neuropsychiatric symptoms in patients with Alzheimer's disease and other forms of dementia.<sup>7</sup>

The International Psychogeriatric Association (IPA) has developed a consensus definition of agitation in patients with cognitive disorders.<sup>5,9</sup>

Provisional Criteria Established

**IN 2015**

Validated

**IN 2023**

- 1** The patient meets criteria for a cognitive impairment or dementia syndrome.<sup>5</sup>
- 2** The patient exhibits  $\geq 1$  behavior grouped under excessive motor activity, verbal or physical aggression, that has been persistent or frequently recurrent for minimum 2 weeks or it represents a dramatic change from the patient's usual behavior.<sup>5\*</sup>
- 3** Behaviors are severe, associated with excess distress or produce excess disability, beyond that due to cognitive impairment.<sup>5</sup>
- 4** While comorbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, medical condition, including delirium, suboptimal care conditions, or the physiological effects of a substance.<sup>5</sup>

\*In special circumstances the ability to document the behaviors over two weeks may not be possible and other terms of persistence and severity may be needed to capture the syndrome beyond a single episode.<sup>5</sup>

# Challenges of the real-world impact and burden on patients and the healthcare system<sup>3</sup> include:



Adverse impact of agitation on patient care, increases the chance of institutionalization, and negatively impacts patient quality of life.<sup>3</sup>



Institutionalization is more than three times higher in agitated than non-agitated patients, and the proportion of institutionalized patients increased with increasing agitation level.<sup>3</sup>



For patients with Alzheimer's dementia and other forms of dementia, medication use is more common in those with agitation vs those without agitation.<sup>3,11</sup>



**56%**

of patients with mild cognitive impairment (CI) report agitation<sup>2</sup>

**75%**

of patients with moderate-to-severe CI report agitation<sup>2</sup>

**68%**

of patients with severe CI report agitation<sup>2</sup>

**53%**

of long-term care residents with dementia present with agitation<sup>11</sup>

**45%**

of those dwelling in the community have agitation symptoms<sup>2</sup>



**Alzheimer's dementia is highly prevalent, under-diagnosed, and predicted to increase significantly in the coming decades due to an aging population.<sup>12</sup>**

### **BY THE NUMBERS**

**In 2023**, there were estimated to be 6.7 million adults in the US aged  $\geq 65$  years living with Alzheimer's dementia<sup>12</sup>

**By 2050**, the number of adults in the US age  $\geq 65$  years living with Alzheimer's dementia in the US is projected to reach 12.7 million<sup>12</sup>

**~1 in 9 people (10.8%) age 65+ has Alzheimer's dementia.<sup>12</sup>**

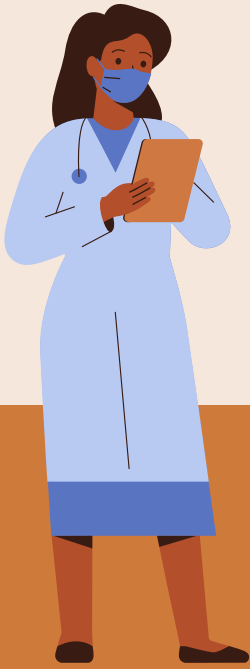
**In 2023, total costs of health care and long-term care for patients with Alzheimer's disease and other forms of dementia were estimated at \$345 billion in the US; the value of informal care-giving was estimated to be \$340 billion.<sup>12</sup>**



### **Agitation in patients with Alzheimer's dementia is associated with high caregiver burden.<sup>13</sup>**

Caretakers of dementia patients, often called "invisible second patients," have a crucial role to play in improving the quality of life of patients. Even though being a family caregiver can sometimes be positive, it is associated with high levels of burden and psychological morbidity, as well as social isolation, medical problems, and financial difficulties.<sup>17</sup> The American Psychiatric Association (APA) guidelines recommend providing individualized interpersonal education and support to caregivers to aid them in coping with challenging behavioral symptoms exhibited by the patient with Alzheimer's dementia who is in their care.<sup>15</sup>

Caregiver stress, burden, depression, culture, and other factors may influence how caregivers report neuropsychiatric symptoms such as agitation.<sup>14</sup> Increased caregiver distress coupled with agitation can lead to institutionalization of patients with Alzheimer's dementia.<sup>10</sup>



## Clinicians and Long-Term Care

Agitation is associated with a higher admission rate to assisted living facilities, higher use of medications, long-term hospitalization, and higher mortality.<sup>27</sup> There is no doubt that the treatment of neuropsychiatric symptoms (NPS) is one of the most challenging aspects of Alzheimer's dementia. Research recommends that pharmacological treatments should only be used when symptoms are severe, dangerous, and/or cause significant distress to the patient. Pharmacological treatments for agitation such as antipsychotics, antidepressants, and benzodiazepines, can be associated with an unfavorable risk/benefit profile.<sup>40,41</sup>

Costs of dementia are high. In 2023, Medicare and Medicaid were expected to cover an estimated \$222 billion, or 64% of the total costs for people with Alzheimer's and other forms of dementia in the US; out-of-pocket costs were estimated to be \$87 billion, or 25% of total costs for people with Alzheimer's and other forms of dementia in the US.<sup>12</sup>

**\$**  
**>x2**

Mean total direct healthcare costs were more than double for patients with agitation in versus patients without agitation (\$20,041 vs \$9,243).<sup>3,18</sup>

**+**  
**20%**

Compared with individuals without agitation, those with agitation were 20% more likely to be institutionalized.<sup>10</sup>

**2050**  
**\$1T**

Costs of health care, long-term care and hospice care for people with Alzheimer's disease and other dementias are projected to increase to nearly \$1 trillion in 2050.<sup>12</sup>

**60%**

of US family caregivers work<sup>12</sup>

**8%**

of caregivers report turning down promotion opportunities<sup>12</sup>

**57%**

of caregivers report needing to arrive late to work or leave early<sup>12</sup>

**Expert guidelines recommend treating agitation with non-pharmacological options and adding pharmacological treatment based on symptoms severity.<sup>8, 15</sup>**



**Per APA guidelines, physicians may prescribe the following:<sup>8,15</sup>**



### **Non-Pharmacological Intervention:**

If agitation does not cause significant danger or marked distress to the patient or others, symptoms are best treated with environmental or behavioral measures.<sup>8,15</sup>



### **Pharmacological Intervention:**

If nonpharmacological measures are unsuccessful or behaviors are dangerous or markedly distressing, then judicious pharmacological intervention is recommended.<sup>8,15</sup>



**Antipsychotics (typical and atypical)**



**Benzodiazepines**



**Anticonvulsants**



**Other Medications**

## Non-Pharmacological Interventions:

Evidence-based nonpharmacological practices have been classified in 3 overarching categories.<sup>28</sup>



## Assessment Scales for Agitation Associated with Alzheimer's Dementia

Several assessment scales are currently available to investigate the presence and severity of agitation and cognitive function:<sup>19-24</sup>

**The Cohen-Mansfield Agitation Inventory (CMAI)** scale is comprised of 29 items which assess agitated behaviors in elderly persons.<sup>19</sup>

CMAI

**Overt Agitation Severity Scale (OASS)** offers a helpful approach to detect and rate the severity of agitation when spanning from anxiety to aggression.<sup>22</sup>

OASS

**The Neuropsychiatric Inventory (NPI)** evaluates 12 neuropsychiatric disturbances common in dementia.<sup>20</sup>

NPI

**The Clinical Global Impression – Severity (CGI-S)** scale was developed to provide an assessment of the clinician's view of the severity of the patient's global functioning.<sup>23</sup>

CGI-S

**The Mini-Mental State Examination (MMSE)**, a clinically validated 11-item assessment, is used to test cognitive function among the elderly and to assess severity of cognitive impairment in patients with Alzheimer's dementia.<sup>21</sup>

MMSE

**The Behavioral Activity Rating Scale (BARS)** is used in clinical trials. Patients are classified into seven distinct levels of agitation.<sup>24</sup>

BARS

## Treatment Plans

**Patients with agitation in Alzheimer’s dementia, and their caregivers, benefit from the development of a comprehensive treatment plan encompassing non-pharmacological and pharmacological interventions, as recommended in current guidelines.<sup>8</sup>**

Per APA guidelines, performing a detailed history and a sound clinical investigation including the patient and their family and care team is pivotal. A person-centered treatment plan should consider the patient’s individual and their environmental risk profile. APA recommends reviewing the clinical response to non-pharmacological interventions prior to pharmacological treatments. With the right level of care and an involved multidisciplinary team, intervention can ameliorate effects and improve the quality of life for both patients and their families.<sup>8,15</sup>

## Pathophysiology of Agitation In Alzheimer’s Dementia

**Agitation in Alzheimer’s dementia is associated with an imbalance between top-down executive control and bottom-up emotional drive.<sup>26,27</sup>**

Research has shown that tau pathology and neurodegeneration in key prefrontal and subcortical brain regions may increase the risk of developing agitation in Alzheimer’s dementia.<sup>35,42-44</sup>

Hypoactivity has been observed in prefrontal regions, including the dlPFC, vmPFC, and OFC,<sup>29-31</sup> along with hyperactivity in subcortical brain regions, including the amygdala.<sup>32</sup> Hyperactivity in the norepinephrine system can lead to impaired executive control along with increased emotional drive.<sup>34</sup> The dopamine system may remain relatively preserved,<sup>25</sup> although serotonin deficits can increase striatal dopamine,<sup>36</sup> which may lead to agitation.<sup>37</sup> Serotonin system deficits<sup>25</sup> may alter PFC regulation of the amygdala,<sup>38</sup> causing increased aggression and impulsivity.<sup>39</sup>



**Abbreviations:** dlPFC, dorsolateral PFC; OFC, orbitofrontal cortex; PFC, prefrontal cortex; vmPFC, ventromedial PFC

Alzheimer’s dementia is highly prevalent, under-diagnosed, and predicted to increase significantly in the coming decades due to an aging population (2023 Alzheimer’s disease facts and figures. Alzheimer’s Dementia 2023;:10.1002/alz.13016).<sup>12</sup>

In the webinar, [“A Conversation With An Expert In Agitation In Alzheimer’s Dementia, A Person With Lived Experience, & A Care Partner”](#), panelists discuss special considerations and experience of agitation in AD.



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