



# Burden and Treatment Considerations for Agitation Associated with Alzheimer's Dementia

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# Our Featured Speakers



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Otsuka Pharmaceutical Development and  
Commercialization

# Objectives

Review the patient, caregiver, and economic burden related to agitation associated with Alzheimer's Disease (AAD)



List the currently available treatment recommendations and guidelines for AAD



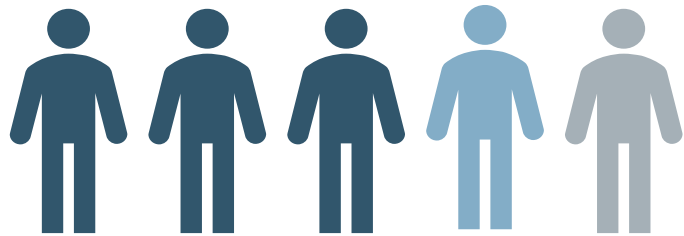
Identify gaps in current treatment options, both pharmacologic and nonpharmacologic

# Patient, Caregiver, and Economic Burden

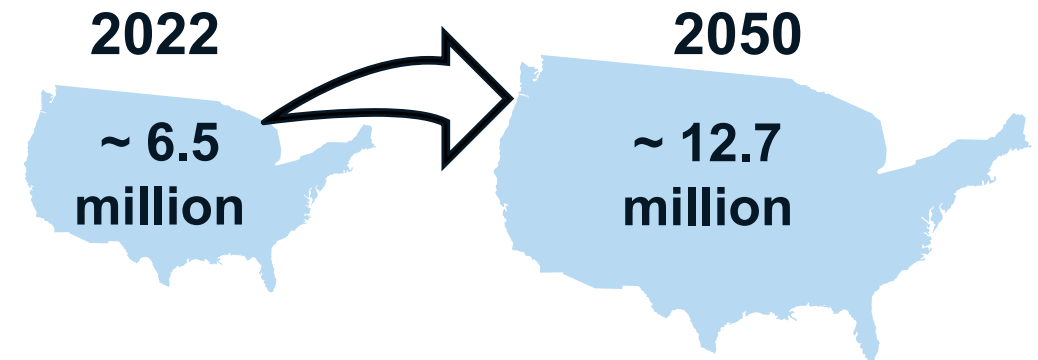
Agitation Associated with Alzheimer's Dementia

Alzheimer's disease is highly prevalent, under-diagnosed, and predicted to increase significantly in the coming decades due to an aging population

**Alzheimer's disease contributes to 60% to 80% of dementia cases**



**In the USA people  $\geq 65$  years with Alzheimer's dementia**

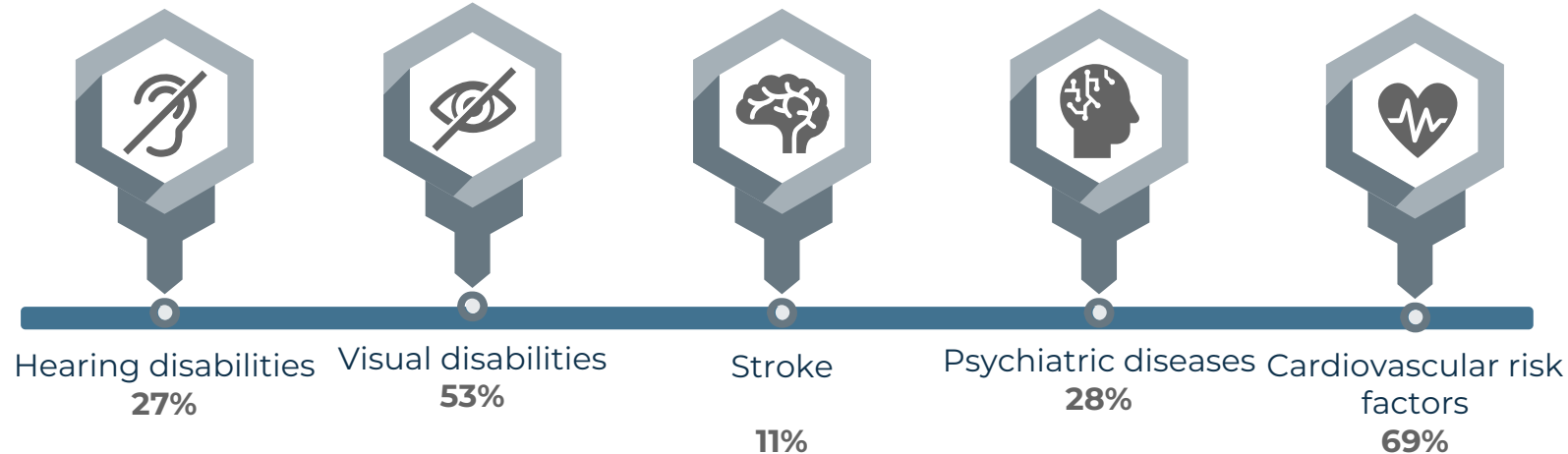


- Many people living with Alzheimer's disease are either undiagnosed or unaware of the diagnosis, with even higher rates among racial or ethnic minorities

1. Alzheimer's Association. (2022). 2022 Alzheimer's disease facts and figures. *Alzheimer's Dementia*, 18(4), 700-789. doi:10.1002/alz.12638.

# AAD is associated with substantial patient burden and long-term consequences

- Patients with Alzheimer's disease and clinically significant agitation have a range of comorbidities<sup>1</sup>
- In 262 patients with AAD, comorbidities included:<sup>1</sup>



**In patients with dementia, behavioral disturbances including agitation are associated with increased comorbidities, compared with those without behavioral disturbances<sup>2</sup>**

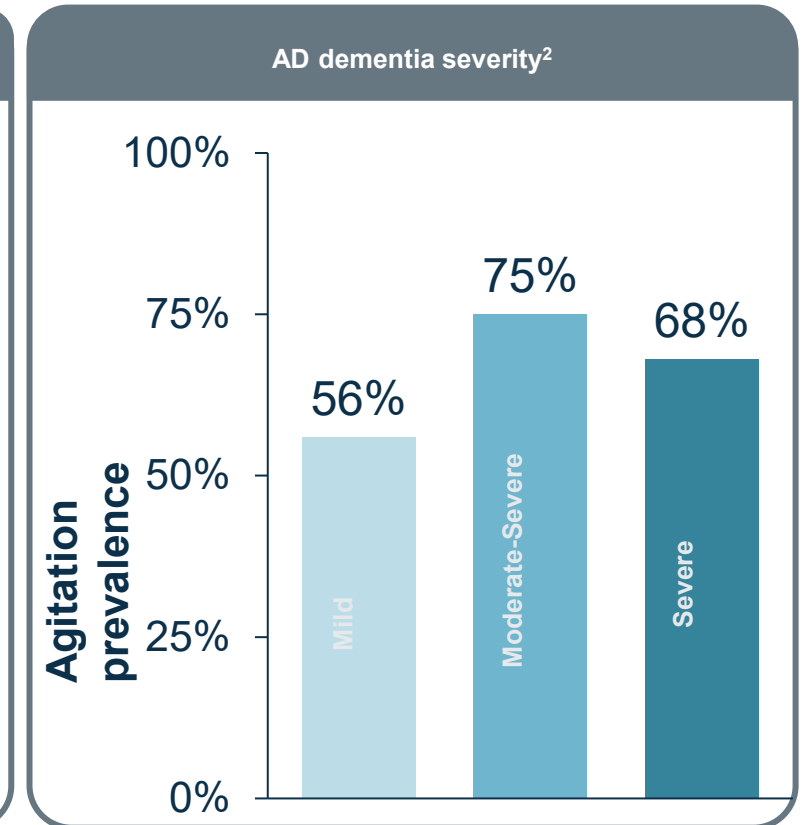
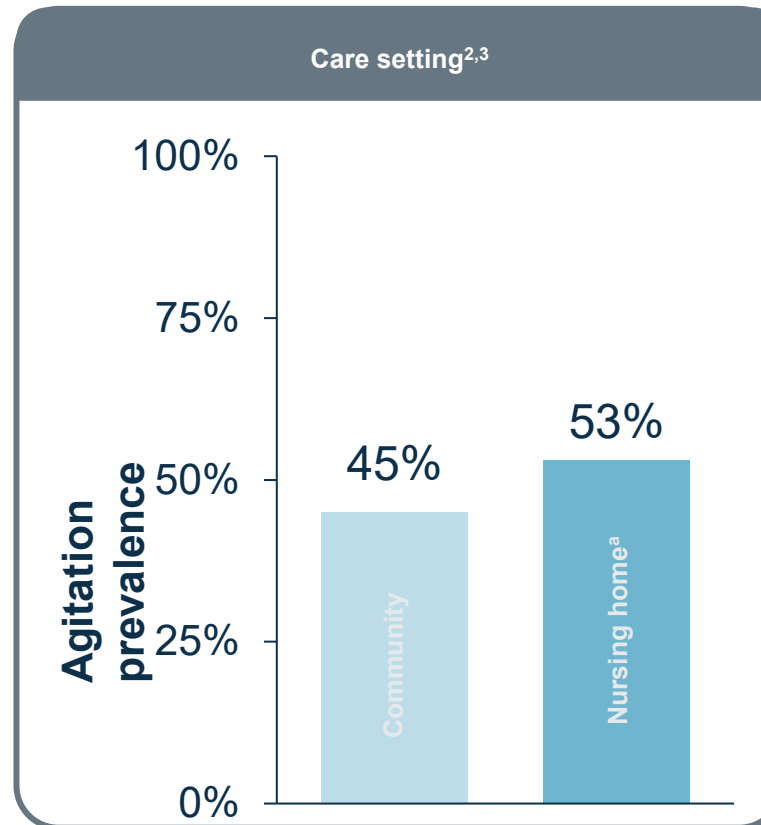
AAD, agitation associated with Alzheimer's dementia.

1. De Mauleon, A., Delrieu, J., Cantet, C., Vellas, B., Andrieu, S., Rosenberg, P. B., Soto Martin, M. (2021). Longitudinal course of agitation and aggression in patients with Alzheimer's disease in a cohort study: Methods, Baseline and longitudinal results of the A3C study. *Journal of Prevention of Alzheimer's Disease*, 8(2), 199-209. doi:10.14283/jpad.2020.66
2. Aigbogun, M. S., Stellhorn, R., Hartry, A., Baker, R. A., & Fillit, H. (2019). Treatment patterns and burden of behavioral disturbances in patients with dementia in the United States: a claims database analysis. *BMC Neurology*, 19(1), 33



# Agitation is a common neuropsychiatric symptom of Alzheimer's dementia and highly prevalent across patient settings and Alzheimer's disease severities

Manifestations of Alzheimer's dementia are not limited to cognitive symptoms and include a range of neuropsychiatric symptoms, including agitation, which when present are experienced alongside the hallmark disease characteristics of memory loss and cognitive decline<sup>1</sup>



<sup>a</sup>Nursing home percentage reported includes those with AD and other dementias. AD, Alzheimer's disease.

1. Kales, H. C., Gitlin, L. N., & Lyketsos, C. G. (2015). Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*, 350.

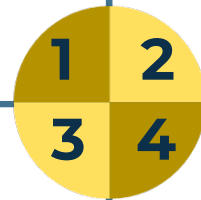
2. Halpern, R., Seare, J., Tong, J., Hartry, A., Olaoye, A., & Aigbogun, M. S. (2019). Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. *International Journal of Geriatric Psychiatry*, 34(3), 420-431.

3. Fillit, H., Aigbogun, M. S., Gagnon-Sanschagrin, P., Cloutier, M., Davidson, M., Serra, E., Grossberg, G. (2021). Impact of agitation in long-term care residents with dementia in the United States. *International Journal of Geriatric Psychiatry*, 36(12), 1959-1969.

# The International Psychogeriatric Association (IPA) has developed a provisional consensus definition of agitation in patients with cognitive disorders

The consensus definition for agitation in cognitive disorders includes 4 definitions:

<p><b>Criteria for cognitive impairment or dementia syndrome</b></p> <p>Patients must meet criteria for a cognitive impairment or dementia syndrome including:</p> <ul style="list-style-type: none"><li>• Alzheimer's disease</li><li>• Mild cognitive impairment</li><li>• Other dementias</li></ul>	<p><b>Agitation behavior &amp; duration</b></p> <ul style="list-style-type: none"><li>• Patient must exhibit <math>\geq 1</math> agitation behavior associated with emotional distress</li><li>• Behavior must be persistent or frequently recurrent for <math>\geq 2</math> weeks</li><li>• Must represent a change from the patient's usual behavior</li></ul>
<p><b>Agitation behavior severity</b></p> <p>Behavior must be severe enough to produce excess disability, beyond that due to the cognitive impairment<sup>a</sup> and significantly impair <math>\geq 1</math> of the following:</p> <ul style="list-style-type: none"><li>• Interpersonal relationships</li><li>• Other aspects of social functioning</li><li>• Ability to perform or participate in daily living activities</li></ul>	<p><b>Agitation behavior cause</b></p> <p>Agitation cannot be attributable solely to:</p> <ul style="list-style-type: none"><li>• Another psychiatric disorder</li><li>• Suboptimal care conditions</li><li>• Medical condition</li><li>• Physiological effects of a substance</li></ul>



<sup>a</sup>According to the clinician's opinion. IPA, International Psychogeriatric Association.

1. Cummings, J., Mintzer, J., Brodaty, H., Sano, M., Banerjee, S., Devanand, D., Lyketsos, C. G. (2015). Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*, 27(1), 7-17.

# The IPA defines 3 agitation behavior domains associated with emotional distress

- The IPA defines agitation in Alzheimer's dementia as excessive motor activity, verbal aggression, or physical aggression. Examples of each include the following behaviors:

## Excessive motor activity behaviors:

- Pacing
- Rocking
- Gesturing
- Pointing fingers
- Restlessness
- Performing repetitious mannerisms



## Verbal aggression behaviors:

- Yelling
- Speaking in an excessively loud voice
- Using profanity
- Screaming
- Shouting



## Physical aggression behaviors:

- Grabbing
- Shoving
- Pushing
- Resisting
- Hitting others
- Kicking objects or people
- Scratching
- Biting
- Throwing objects
- Hitting self
- Slamming doors
- Tearing things
- Destroying property



IPA, International Psychogeriatric Association.

1. Cummings, J., Mintzer, J., Brodaty, H., Sano, M., Banerjee, S., Devanand, D., Lyketsos, C. G. (2015). Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*, 27(1), 7-17.

# AAD worsens the impact of an already devastating and burdensome disease

- Agitation in long-term care residents with Alzheimer's disease and other forms of dementia has been associated with:

**Numerically higher medication use with agitation**

**5** median medications with agitation vs **4** without agitation

**An increased likelihood compared with patients without agitation of:**

**Infections**



**18%** more likely with agitation

**Fractures**



**29%** more likely with agitation

**Falls**



**58%** more likely with agitation

**Other neuropsychiatric symptoms<sup>a</sup>**



**111%** more likely with agitation

<sup>a</sup>Additional neuropsychiatric symptoms include depression, anxiety, delusion, and hallucinations. AAD, agitation associated with Alzheimer's dementia.

1. Fillit, H., Aigbogun, M. S., Gagnon-Sanschagrin, P., Cloutier, M., Davidson, M., Serra, E., Crossberg, G. (2021). Impact of agitation in long-term care residents with dementia in the United States. *International Journal of Geriatric Psychiatry*, 36(12), 1959-1969. doi:10.1002/gps.5604

# AAD is associated with substantial patient burden and long-term consequences

**Compared with nonagitated patients with early cognitive impairment or Alzheimer's disease dementia,<sup>a</sup> agitation is associated with increased:**



## Hospitalization

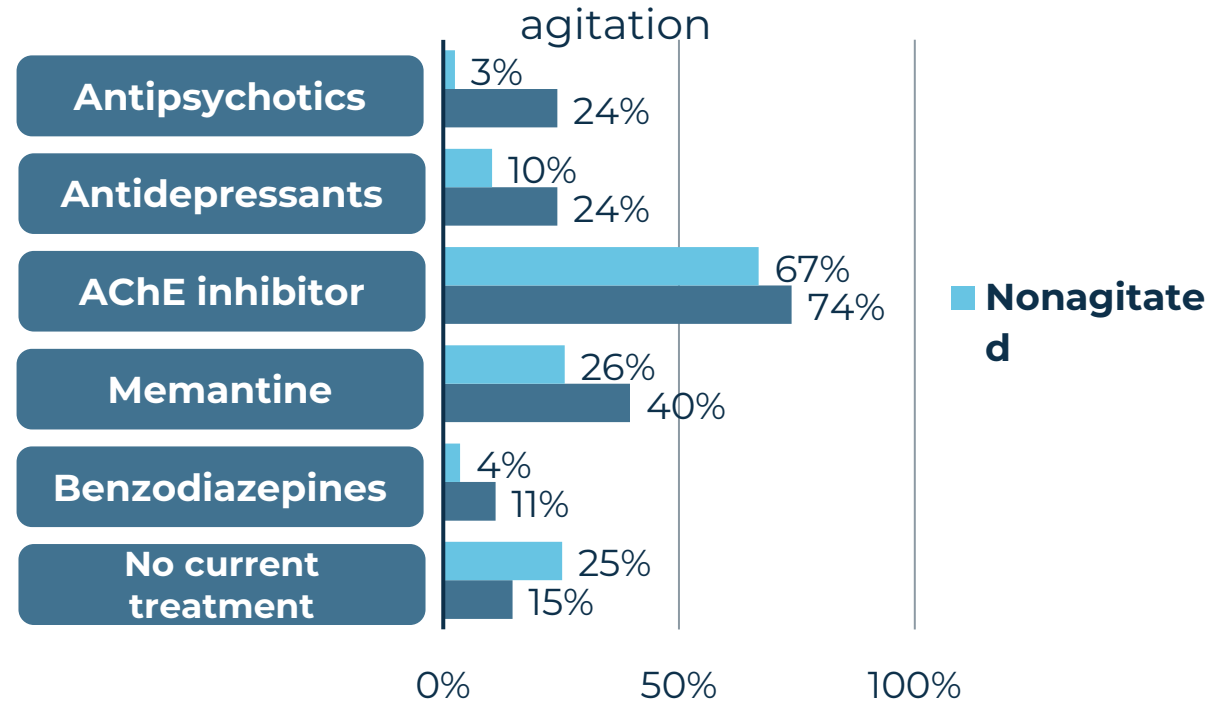
**2x more mean visits** in those with agitation vs without agitation



## Institutionalization

**3.7x higher rate** in those with agitation vs without agitation

In those with cognitive impairment or Alzheimer's disease dementia,<sup>a</sup> current medication use is more common in those with agitation vs those without

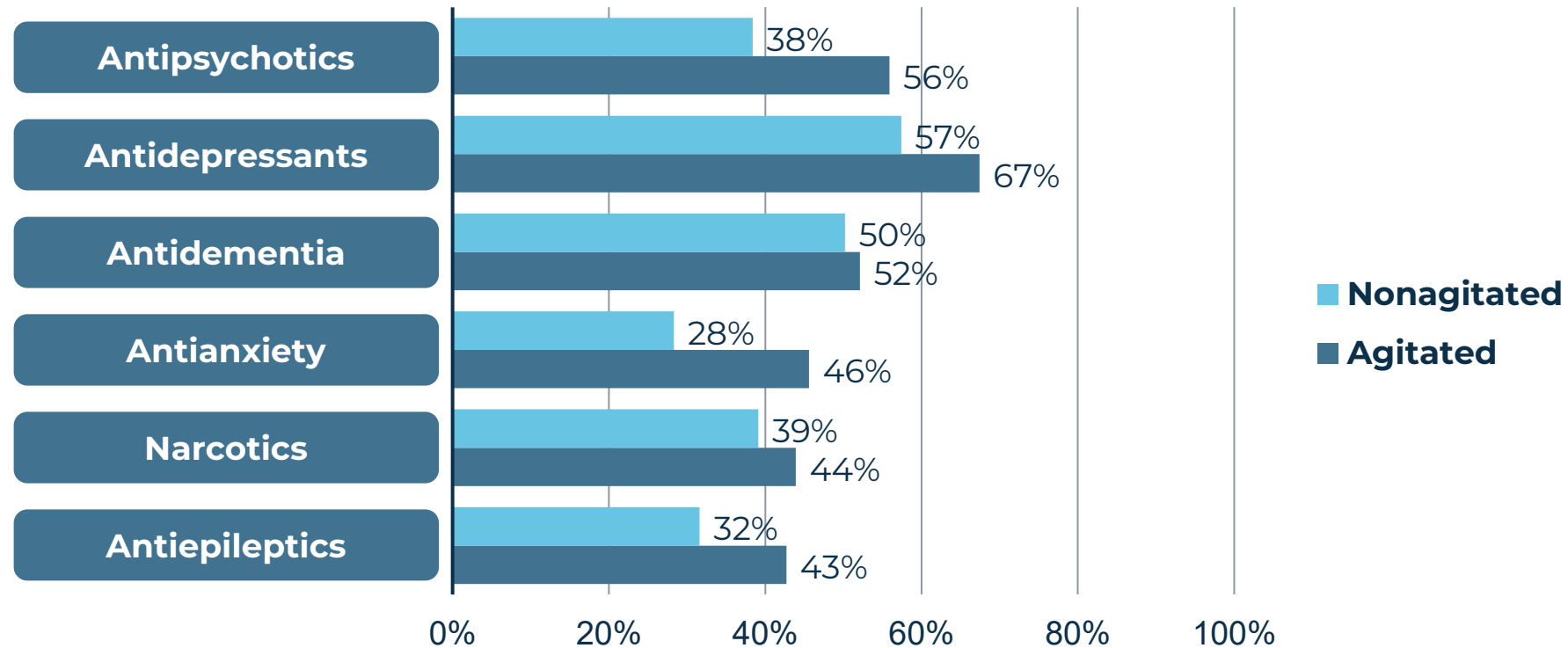


<sup>a</sup>Including mixed Alzheimer's disease and vascular dementia.  
AChE, acetylcholinesterase.

1. Jones, E., Aigbogun, M. S., Pike, J., Berry, M., Houle, C. R., & Husbands, J. (2021). Agitation in dementia: real-world impact and burden on patients and the healthcare system. *Journal of Alzheimer's Disease*, 83(1), 89-101. doi:10.3233/jad-210105

# AAD is associated with substantial patient burden and long-term consequences

- In long-term care patients with Alzheimer's disease dementia and other forms of dementia, medication use is more common in those with agitation vs those without agitation



AAD, agitation associated with Alzheimer's dementia.

1. Fillit, H., Aigbogun, M. S., Gagnon-Sanschagrin, P., Cloutier, M., Davidson, M., Serra, E., Grossberg, G. (2021). Impact of agitation in long-term care residents with dementia in the United States. *International Journal of Geriatric Psychiatry*, 36(12), 1959-1969. doi:10.1002/gps.5604

# AAD is associated with an increased economic burden for both healthcare systems and individuals

- In a real-world study of 1,349 patients with early cognitive impairment or Alzheimer's dementia, patients identified as having agitation demonstrated significantly higher healthcare resource utilization and costs than patients without agitation

**Increased rates of institutionalization**

**Increased rates of hospitalization**

**More consultations with a healthcare professional**

**A higher overall cost**

	<b>Nonagitated</b>	<b>Agitated</b>
Percentage institutionalized	3.2%	11.9%
Mean number of hospitalizations for any reason in the past 12 months	0.2	0.4
Mean number of consultations with any HCP in the past 12 months	4.3	6.5
Mean total direct healthcare costs	\$9,243	\$20,041

AAD, agitation associated with Alzheimer's dementia; HCP, healthcare professional.

1. Jones, E., Aigbogun, M. S., Pike, J., Berry, M., Houle, C. R., & Husbands, J. (2021). Agitation in dementia: real-world impact and burden on patients and the healthcare system. *Journal of Alzheimer's Disease*, 83(1), 89-101. doi:10.3233/jad-21010

# Agitation in patients with Alzheimer's dementia is associated with high caregiver burden



Symptoms of agitation in patients with dementia can be a source of embarrassment and anxiety for caregivers<sup>1</sup>



The presence of neuropsychiatric symptoms such as agitation relates to caregiver burden, with the burden of care increasing with severity of agitation<sup>2-5</sup>

## Agitation & caregiver burden

Informal caregivers of patients with cognitive impairment or dementia **spend more than 20 additional hours per week** actively helping patients with clinically significant agitation<sup>5</sup>



Increased caregiver distress coupled with agitation can lead to institutionalization of patients with dementia<sup>5</sup>



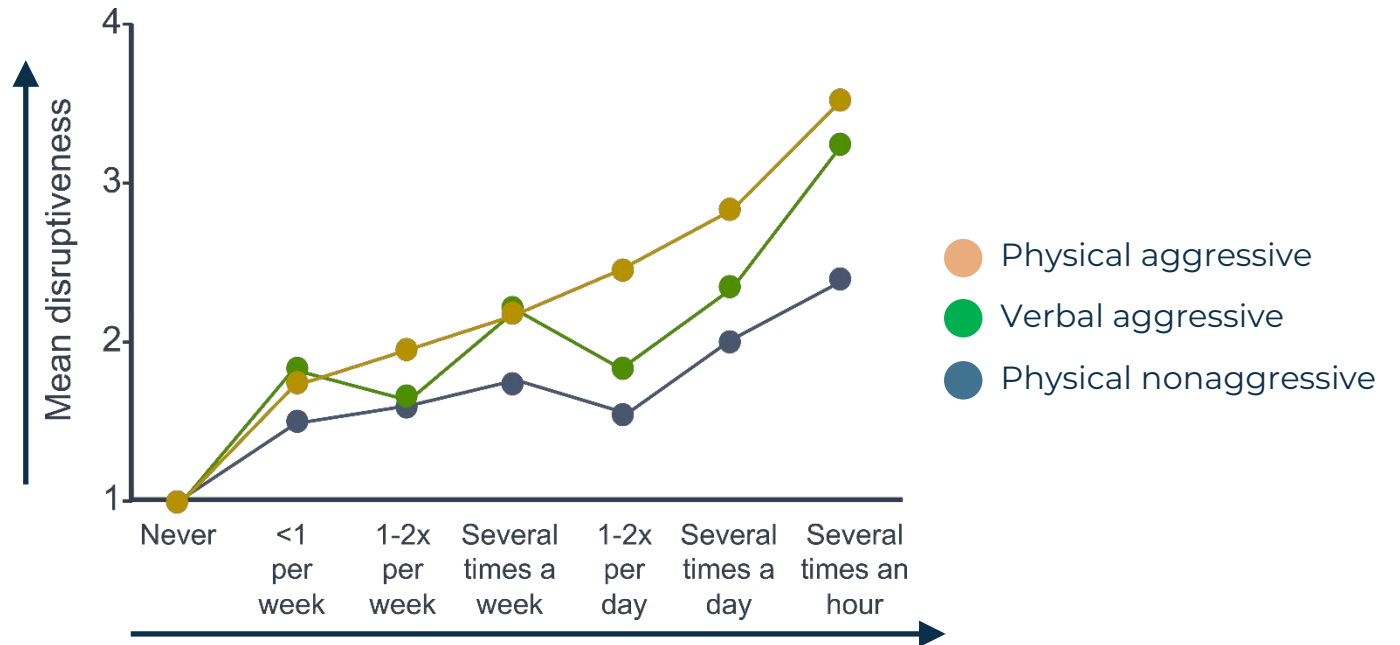
1. Cohen-Mansfield, J. (2008). Agitated behavior in persons with dementia: the relationship between type of behavior, its frequency, and its disruptiveness. *Journal of Psychiatric Research*, 43(1), 64-69. doi:10.1016/j.jpsychires.2008.02.003
2. Allegri, R. F., Sarasola, D., Serrano, C. M., Taragano, F. E., Arizaga, R. L., Butman, J., & Loñ, L. (2006). Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 2(1), 105-110
3. Grossberg, G. T., Kohegyi, E., Mergel, V., Josiassen, M. K., Meulien, D., Hobart, M., . . . Cummings, J. L. (2020). Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. *The American Journal of Geriatric Psychiatry*, 28(4), 383-400. doi:10.1016/j.jagp.2019.09.009
4. Mohamed, S., Rosenheck, R., Lyketsos, C. G., & Schneider, L. S. (2010). Caregiver burden in Alzheimer disease: cross-sectional and longitudinal patient correlates. *The American Journal of Geriatric Psychiatry*, 18(10), 917-927. doi:10.1097/JGP.0b013e3181d5745d
5. Okura, T., & Langa, K. M. (2011). Caregiver burden and neuropsychiatric symptoms in older adults with cognitive impairment: the Aging, Demographics, and Memory Study (ADAMS). *Alzheimer Disease and Associated Disorders*, 25(2), 116-121. doi:10.1097/WAD.0b013e318203f208



# Agitation in patients with Alzheimer's dementia is associated with high caregiver burden

- Among professional caregivers in nursing homes for people with dementia, agitation was associated with the highest mean distress score among neuropsychiatric symptoms, and the score increased with symptom severity<sup>1</sup>

In nursing homes caring for people with dementia, the disruptiveness of agitated behaviors measured using the Cohen-Mansfield Agitation Inventory (CMAI) increases with frequency for all behavior types<sup>2</sup>



CMAI, Cohen-Mansfield Agitation Inventory.

1. Zwijsen, S. A., Kabboord, A., Eefsting, J. A., Hertogh, C. M., Pot, A. M., Gerritsen, D. L., & Smalbrugge, M. (2014). Nurses in distress? An explorative study into the relation between distress and individual neuropsychiatric symptoms of people with dementia in nursing homes. *International Journal of Geriatric Psychiatry*, 29(4), 384-391. doi:10.1002/gps.4014
2. Cohen-Mansfield, J. (2008). Agitated behavior in persons with dementia: the relationship between type of behavior, its frequency, and its disruptiveness. *Journal of Psychiatric Research*, 43(1), 64-69. doi:10.1016/j.jpsychires.2008.02.003

# Treatment & Current Treatment Guidelines

## Agitation Associated with Alzheimer's Dementia

# Individualized and multimodal treatment plans are recommended for patients with Alzheimer's Disease

The American Psychiatric Association guidelines recommend that the treatment of patients with Alzheimer's and other dementias should:



Be based on thorough psychiatric and general medical evaluation



Include evaluation of the nature and cause of the cognitive deficits and associated noncognitive symptoms



Be in the context of a solid alliance with the patient and family

1. Rabins, P. V., et al.(2007). *The American Journal of Psychiatry*, 164(12 Suppl), 5-56.
2. Reus, V. I., et al.. (2016). American Psychiatric Association. <https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890426807>

# Guidelines for a comprehensive management plan

## Differential diagnosis<sup>1,2</sup>

Careful evaluation and treatment for general medical, psychiatric, environmental, or psychosocial problems that may underlie the disturbance

## Nonpharmacological intervention<sup>1,2</sup>

If agitation does not cause significant danger or distress to the patient or others, symptoms are best treated with environmental or behavioral measures including:

- Behavioral management therapy or behavioral interventions
- Emotion-oriented approaches
- Stimulation-oriented treatments (recreational activity, art therapy, music therapy, and pet therapy)

## Pharmacological intervention<sup>1,2</sup>

If nonpharmacological measures are unsuccessful or behaviors are dangerous or distressing, then judicious pharmacological intervention is recommended:

- Antipsychotics are a pharmacological therapy recommended by the APA for agitation in dementia
- The Harvard South Shore Program also recommends antipsychotics for more than moderately disruptive agitation<sup>3</sup>

APA, American Psychiatric Association.

1. Rabins, P. V., et al. (2007). The American Journal of Psychiatry, 164(12 Suppl), 5-56.
2. Reus, V. I., et al. (2016). The American Journal of Psychiatry, 173(5), 543-546. doi:10.1176/appi.ajp.2015.173501.
3. Chen, A., et al. (2021). Psychiatry Research, 295, 113641. doi:10.1016/j.psychres.2020.113641.

# There is an unmet need for FDA-approved treatments for AAD

- As there are currently no FDA-approved pharmacological treatments for agitation in Alzheimer's dementia, clinicians prescribe off-label use of the following to control behavioral symptoms:<sup>1-3</sup>
  - Antipsychotics
  - Antidepressants
  - Anxiolytics or sedative-hypnotics

Some current treatment options are associated with only modest efficacy and relatively poor safety and tolerability profiles<sup>1,2</sup>

FDA, US Food and Drug Administration.

1. Aigbogun, M. S., et al. (2020). *Journal of Alzheimer's Disease*, 77(3), 1181-1194. doi:10.3233/jad-200127.
2. Schneider, L. S., et al. (2006). *American Journal of Geriatric Psychiatry*, 14(3), 191-210. doi:10.1097/01.JGP.0000200589.01396.6d.
3. Rabins, P. V., et al. (2007). *The American Journal of Psychiatry*, 164(12 Suppl), 5-56.

# Antipsychotics have not been approved by the FDA for treatment of agitation in Alzheimer's dementia

- The APA guidelines and Harvard South Shore Program treatment algorithm indicate that antipsychotics should be a pharmacological treatment for agitation that is severe or does not respond to nonpharmacological therapies<sup>1,2</sup>
- The APA recommendation is based on short-term community and nursing home trials as well as considerable clinical experience<sup>1</sup>

- The efficacy and safety profiles of second-generation antipsychotics for behavioral symptoms in dementia vary based on receptor binding profiles that may target<sup>3</sup>
  - Norepinephrine
  - Serotonin
  - Dopamine
  - Histamine
  - Acetylcholine

APA, American Psychiatric Association; FDA, US Food and Drug Administration.

1. Rabins, P. V., et al. (2007). *The American Journal of Psychiatry*, 164(12 Suppl), 5-56. 2
2. Chen, A., et al. (2021). *Psychiatry Research*, 295, 113641. doi:10.1016/j.psychres.2020.113641.
3. Ma, H., et al. (2014). *Journal of Alzheimer's disease*, 42(3), 915-937. doi:10.3233/JAD-140579.

# Pharmacological treatments for agitation risk/benefit profile

## Benzodiazepines

- Benzodiazepines have modest benefit treating agitation associated with Alzheimer's dementia, but are occasionally used when anxiety is prominent<sup>1</sup>
- Safety concerns with benzodiazepines and their use in the management of agitation particularly in the elderly, include potential:<sup>2</sup>



Risk of cognitive impairment



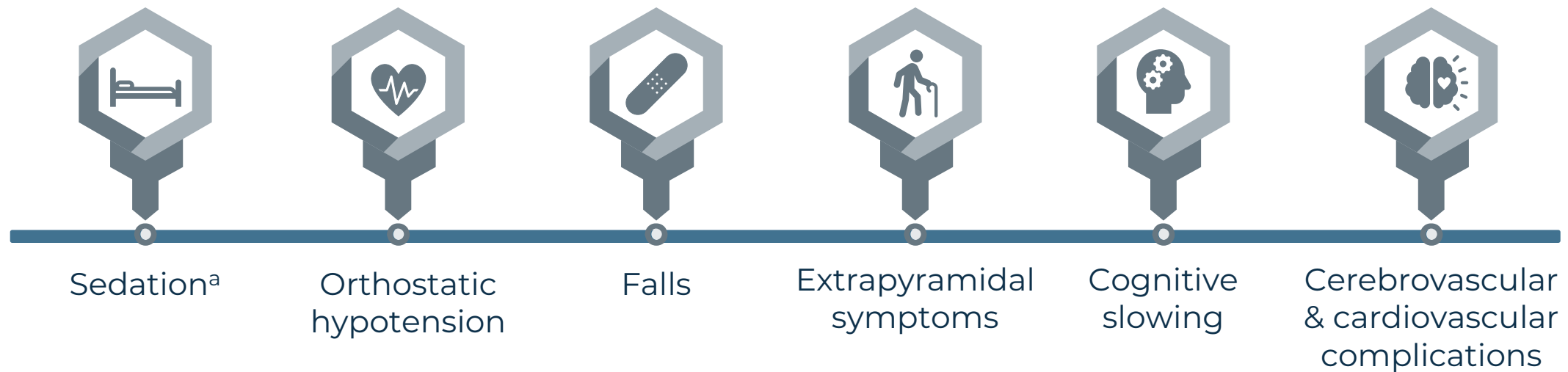
Increased risk of fractures and falls

## Antidepressants

- There is limited evidence to support the use of antidepressants for the treatment of agitation and aggression in dementia<sup>3,4</sup>
- Antidepressants are tolerated reasonably well, however, future studies are required to determine if antidepressants are safe treatments for agitation in Alzheimer's dementia<sup>4</sup>

1. Rabins, P. V., et al. (2007). *The American Journal of Psychiatry*, 164(12 Suppl), 5-56.
2. Defrancesco, M., et al. (2015). *The International Journal of Neuropsychopharmacology*, 18(10), pyv055. doi:10.1093/ijnp/pyv055.
3. Porsteinsson, A. P., et al. (2014). *JAMA*, 311(7), 682-691. doi:10.1001/jama.2014.93.
4. Seitz, D. P., et al. (2011). *Cochrane Database Systematic Reviews* (2), Cd008191. doi:10.1002/14651858.CD008191.pub2.

# Pharmacological treatments for agitation in Alzheimer's dementia can be associated with adverse events



<sup>a</sup>Some family caregivers of patients with Alzheimer's disease and other forms of dementia find sedative effects distressing and unhelpful<sup>4</sup>

1. Schneider, L. S., Dagerman, K., & Insel, P. S. (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry*, 14(3), 191-210. doi:10.1097/01JGP.0000200589.01396.6d. 2. Caraci, F., Santagati, M., Caruso, G., Cannavò, D., Leggio, G. M., Salomone, S., & Drago, F. (2020). New antipsychotic drugs for the treatment of agitation and psychosis in Alzheimer's disease: focus on brexpiprazole and pimavanserin. *Fl000Research*, 9. doi:10.12688/fl000research.22662.1.3. Marcinkowska, M., Sniecikowska, J., Fajkis, N., Paško, P., Franczyk, W., & Kolačzkowski, M. (2020). Management of Dementia-Related Psychosis, Agitation and Aggression: A Review of the Pharmacology and Clinical Effects of Potential Drug Candidates. *CNS drugs*, 34(3), 243-268. <https://doi.org/10.1007/s40263-020-00707-7>. 4. Harding, R., & Peel, E. (2012). 'He was like a zombie': Off-label prescription of antipsychotic drugs in dementia. *Medical Law Review*, 21(2), 243-277. doi:10.1093/medlaw/fws029.



# Summary of the unmet need

- Current guidelines recommend a comprehensive treatment plan for AAD that may include nonpharmacological and pharmacological treatments<sup>1,2</sup>
- There are currently no FDA-approved pharmacological treatments for AAD<sup>2</sup>
- Pharmacological treatments for agitation are associated with mixed risk/benefit profiles<sup>1</sup>

**There is a need for approved pharmaceutical treatments that demonstrate both efficacy and safety in the treatment of agitation in Alzheimer's dementia and that also address the pathophysiology of agitation in Alzheimer's dementia<sup>3</sup>**

AAD, agitation associated with Alzheimer's dementia; FDA, US Food and Drug Administration.

1. Rabins, P. V., et al. (2007). *The American Journal of Psychiatry*, 164(12 Suppl), 5-56.
2. Chen, A., et al. (2021). *Psychiatry Research*, 295, 113641. doi:10.1016/j.psychres.2020.113641.
3. Caraci, F. Et al. (2020). *F1000Research*, 9. doi:10.12688/f1000research.22662.1.

# Closing

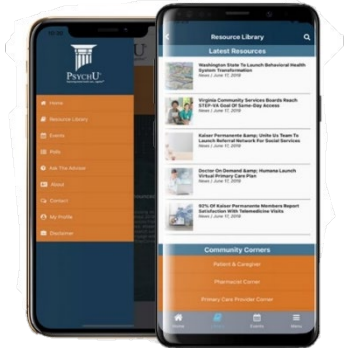
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