



# Disease State Education: Treatment & Current Treatment Guidelines

## Agitation Associated with Alzheimer's Dementia

This program is paid for by Otsuka  
Pharmaceutical Development &  
Commercialization, Inc. (OPDC)

# 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>

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

**The American Psychiatric Association guidelines recommend:**

## Caregiver Integration & Comprehensive Plan

APA guidelines recommend a documented comprehensive treatment plan for agitation in patients with dementia that includes ongoing consideration of the caregiver's preferences, values, concerns, and time

## Individualized Support

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 disease who is in their care

APA, American Psychiatric Association.

1. Reus, V. I., et al. (2016).. American Psychiatric Association. <https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890426807>

# Comprehensive treatment plans may include nonpharmacological and pharmacological interventions

**The following guidelines recommend treating agitation and other behavioral symptoms with nonpharmacological interventions and adding pharmacological interventions when indicated**

<b>APA</b>	<p>The 2007 APA practice guideline for the treatment of patients with Alzheimer's disease and other dementias<sup>1</sup></p> <p>The 2016 APA practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia<sup>2</sup></p>
<b>Harvard South Shore Program</b>	<p>The 2021 Harvard South Shore Program updated treatment algorithm for behavioral and psychological symptoms in dementia<sup>3</sup></p>
<b>AAN</b>	<p>The 2018 AAN guidelines for mild cognitive impairment<sup>4</sup></p>

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.
4. Petersen, R. C., et al.(2018). *Neurology*, 90(3), 126-135. doi:10.1212/WNL.0000000000004826.

# 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

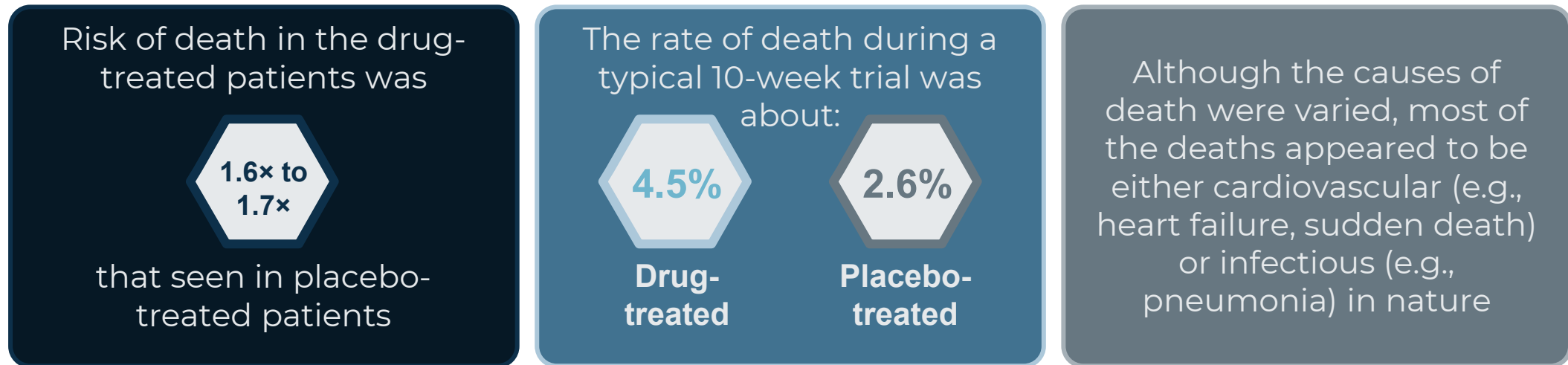
APA, American Psychiatric Association; FDA, US Food and Drug Administration.

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.



# Dementia-related psychosis boxed warning for the antipsychotic drug class

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo<sup>1-6</sup>
- The boxed warning was based on analyses of 17 placebo-controlled trials of aripiprazole, olanzapine, quetiapine, and risperidone (modal duration 10 weeks)<sup>6,7</sup>



- Antipsychotics are not approved for the treatment of patients with dementia-related psychosis<sup>6</sup>

1. Aigbogun, M. S. et al. (2020). *Journal of Alzheimer's Disease*, 77(3), 1181-1194. doi:10.3233/jad-200127. 5. Otsuka America Pharmaceutical, Inc. Abilify (aripiprazole) [package insert]. 2020.  
2. Janssen Pharmaceuticals, Inc. Risperdal (risperidone) [package insert]. 2022. 6. Meeks, T. W., & Jeste, D. V. (2008). Beyond the Black Box: What is The Role for Antipsychotics in Dementia? *Current Psychiatry*, 7(6), 50-65.  
3. AstraZeneca Pharmaceuticals LP. Seroquel (quetiapine) [package insert]. 2022. 7. Schneider, L. S., Dagerman, K. S., & Insel, P. (2005). *JAMA*, 294(15), 1934-1943. doi:10.1001/jama.294.15.1934.  
4. Eli Lilly and Company. Zyprexa (olanzapine) [package insert]. 2021.

# 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



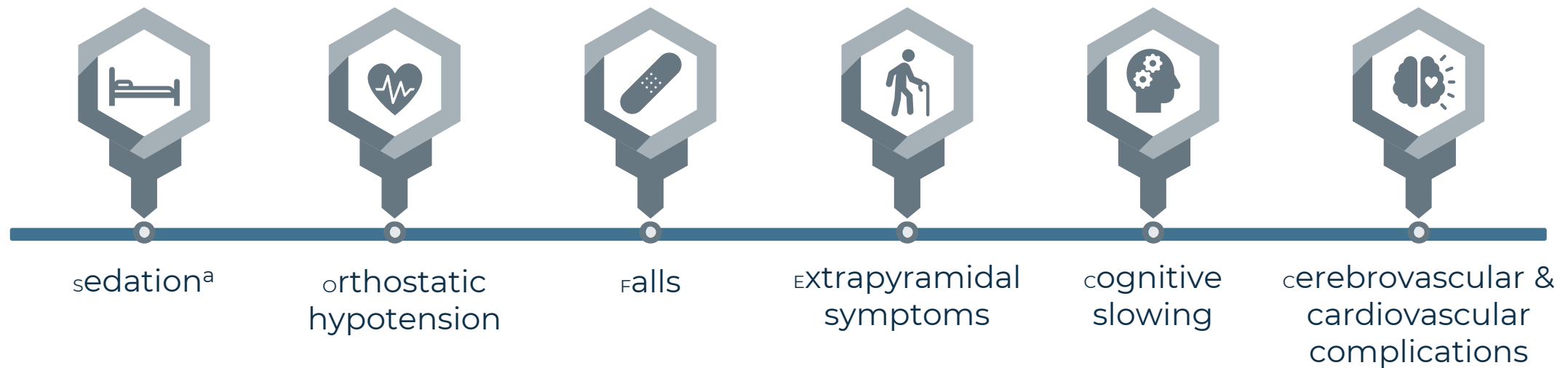
Increased risk of fractures and falls

## 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:10.1097/01.JGP.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. *F1000Research*, 9. doi:10.12688/f1000research.22662.1. 3. Marcinkowska, M., Śniecikowska, J., Fajkis, N., Paśko, P., Franczyk, W., & Kołaczkowski, 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.

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