# Pharmacological management of agitation in Alzheimer's dementia: Rationale and evidence for new and emerging treatment options

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# Expert panel

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# Agenda

- Best practice in the management of agitation in Alzheimer's dementia
- Pathophysiology of agitation in Alzheimer's dementia and new approaches to treatment
- Advances in treatment of agitation in Alzheimer’s dementia: A discussion of the first approved therapy and novel approaches on the horizon

# Best practice in the management of agitation in Alzheimer's dementia

# Managing people living with AAD: The IPA approach

## Investigate

- **Understand the behaviour**
  - Does it meet IPA criteria for agitation?
  - What are the patient's characteristics?
  - When do episodes occur?
  - What precipitates episodes?
  - What is the duration and frequency of episodes?
  - Is there potential for harm?

## Plan

- **Construct an intervention that reflects the patient and their setting**
- **Share the process of decision-making with the patient and care partner**

## Act

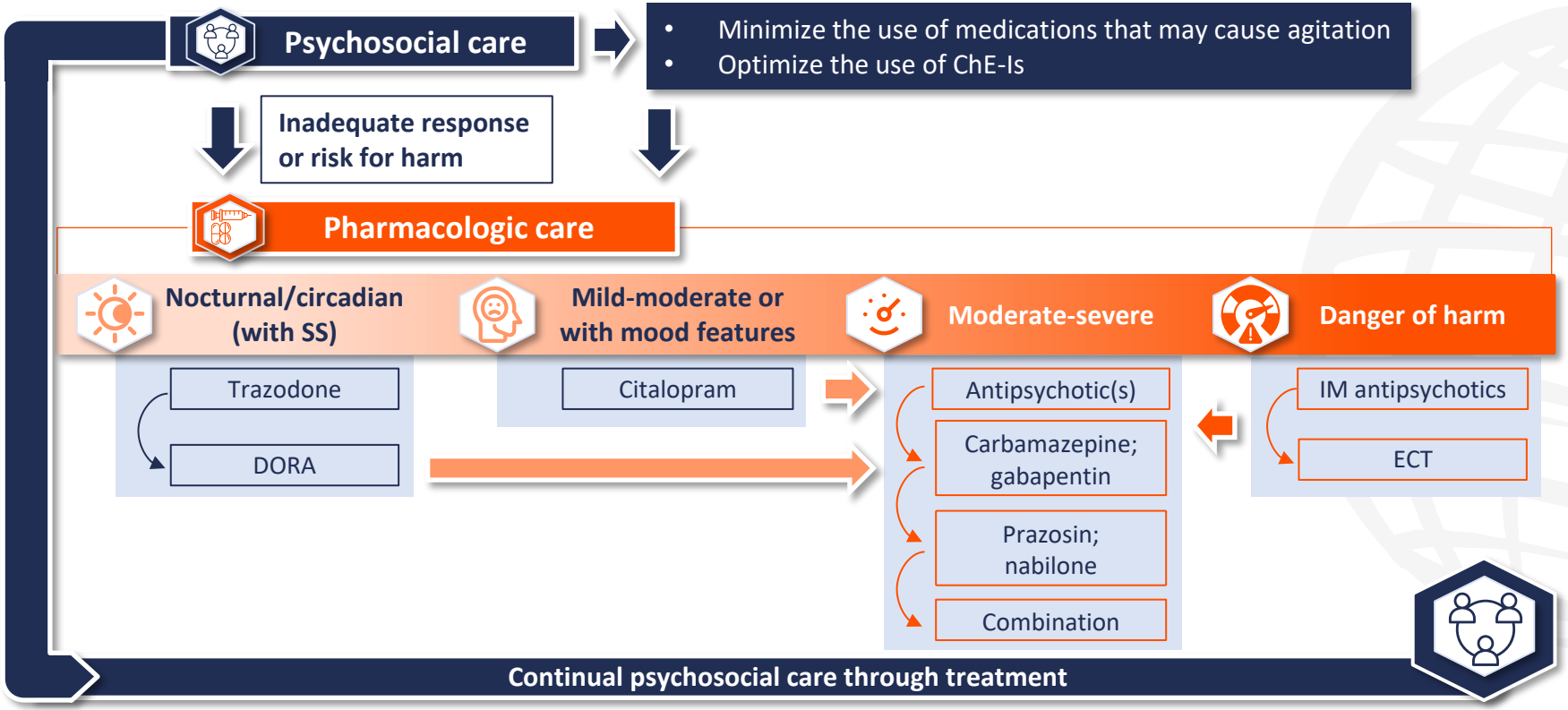
- **Implement the MDT care plan with defined responsibilities for all team members**
- **Implement all appropriate psychosocial interventions**
- **Choose a pharmacologic strategy as appropriate**

## Post-intervention

- **Determine the effect of any intervention on the agitation**
- **Establish if the response is partial or full**
- **Evaluate for any AEs of pharmacotherapy**

AE, adverse effects; AAD, agitation in Alzheimer's dementia; IPA, Investigate, Plan and Act; AE, adverse effects; MDT, multidisciplinary team.
Cummings J, et al. *Int Psychogeriatr*. 2024;36:251–62.

# The IPA agitation treatment algorithm




CHE-I, cholinesterase inhibitor; DORA, dual orexin receptor antagonist; ECT, electroconvulsive therapy; IM, intramuscularly; IPA, Investigate, Plan and Act; SS, sundown syndrome.

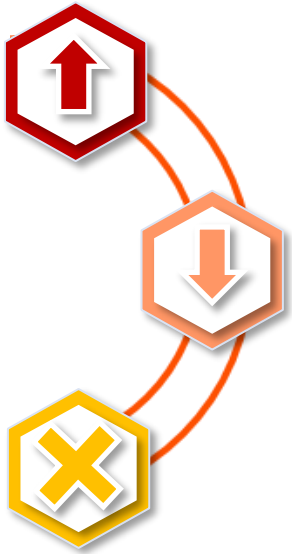
Cummings J, et al. *Int Psychogeriatr*. 2024;36:251–62.

# Pathophysiology of agitation in Alzheimer's dementia and new approaches to treatment

# Neurotransmitter pathways associated with AAD

AAD is a **frontal lobe syndrome,** notably involving abnormal activation of the OFC and ACC[2,10,11]

AAD may reflect dysfunction in the norepinephrine, serotonin, and dopamine neurotransmitter systems[1–3]



- **Norepinephrine system hyperactivity**:[1–6]
  - Heightened emotional drive from the amygdala to the prefrontal cortex
- **Decreased serotonin signalling**:[1,7–9]
  - Impaired cognitive and behavioural control
  - Increased aggression and impulsivity
  - Dysregulation in the dopamine system
- **Dysregulated dopamine activity**:[1–3]
  - Increased risk of agitated aggressive/ psychotic behaviours

ACC, anterior cingulate cortex; AAD, agitation in Alzheimer's dementia; OFC, orbitofrontal cortex.
1. Liu KY, et al. *Ageing Res Rev*. 2018;43:99–107; 2. Rosenberg PB, et al. *Mol Aspects Med*. 2015;43–44:25–37; 3. Lindenmayer JP. *J Clin Psychiatry*. 2000;61 (Suppl. 14):5–10;
4. Gannon M, Wang Q. *Brain Res*. 2019;1702:12–6; 5. Szot P, et al. *Neuroscience*. 2007;146:471–80; 6. Gulyás B, et al. *Neurochem Int*. 2010;56:789–98;
7. Vermeiren Y, et al. *Neurobiol Aging*. 2014;35:2691–700; 8. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13:5–21; 9. Solas M, et al. *Neurochem Int*. 2021;150:105185;
10. Carrarini C, et al. *Front Neurol*. 2021;12:644317; 11. Senanarong V, et al. *Dement Geriatr Cogn Disord*. 2004;17:14–20.

# New and emerging therapeutics for AAD: MoA

## AXS-05[1,2]

**Targets and action**

- NMDA receptor antagonist
- Sigma-1 receptor agonist

**Impact**

- Influences mood and behaviour through modulation of NMDA receptors and stimulation of the dopaminergic system

## Brexpiprazole[3]

**Targets and action**

- Noradrenergic $\alpha_{1B}$ and $\alpha_{2C}$ and 5-$HT_{2A}$ receptor antagonist
- Serotonin 5-$HT_{1A}$ and dopamine D2 receptor partial agonist

**Impact**

- Suppression of multiple receptors related to agitation, aggression, impulsiveness, arousal and psychosis

## Nabilone[4,5]

**Targets and action**

- CB1 and CB2 partial agonist

**Potential impact**

- Increased serotonergic signalling
- Neuroprotection through reduced oxidative stress, reduced TNF-α, and reduced glutamate release
- Improved circadian rhythm

Available evidence suggests multiple neurotransmitter systems are involved in AD-related agitation.
An optimal approach may be one that targets multiple receptors from different neurotransmitter systems[6]

5-HT, serotonin receptors; AAD, agitation in AD; AD, Alzheimer's dementia; AXS-05, dextromethorphan-bupropion; CB1/2, cannabinoid receptor type 1/2; D2, dopamine receptor type 2; MoA, mechanism of action; NMDA, N-methyl-d-aspartate; TNF, tumour necrosis factor.

1. Marcinkowska M, et al. *CNS Drugs*. 2020;34:243–68; 2. Cummings J, et al. *Neurology*. 2024;102(17 Suppl. 1):PL5.004; 3. Lee D, et al. *JAMA Neurol.* 2023;80:1307–16; 4. Outen JD, et al. *Am J Geriatr Psychiatry*. 2021;29:1253–63; 5. Sherman C, et al. *Curr Opin Psychiatry*. 2018;31:140–6; 6. Liu KY, et al. *Ageing Res Rev*. 2018;43:99–107.

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# Advances in treatment of agitation in Alzheimer's dementia: A discussion of the first approved therapy and novel approaches on the horizon

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# Efficacy: New and emerging therapies for AAD

| | Approved (FDA 2023)[1,2] | Under investigation | | |
|---|---|---|---|---|
| **Agent** | **Brex (phase III)[3]** | **AXS-05 (phase III)[4]** | **Nabilone** | |
| | | | Phase II[5] | Phase III[6] |
| **Patients** | N=345<br>(Brex: n=228; Pbo: n=114) | OLP: N=178<br>DBP: n=108 responders*<br>(AXS-05: n=53; Pbo: n=55) | N=38<br>(DB crossover) | **NCT04516057**<br>N=112; 16 weeks<br>(Nabilone vs Pbo) |
| **Primary endpoint** | **Mean ΔCMAI (BL–Wk 12)**:<br>Brex: -22.6; Pbo: -17.3<br>Cohen's *d* effect size: 0.35<br>(p=0.003) | **OLP**: Improvement in CMAI (Wk 1–Wk 5, p<0.001)<br>**DBP**: Substantial delay in time to relapse vs Pbo (p=0.014) | **Estimated ΔCMAI**:<br>Cohen's *d* effect size: 0.52 | **Primary endpoint**:<br>ΔCMAI (BL–Wk 8)<br>**Estimated completion**:<br>October 2025 |

Direct comparisons between trials should not be made due to differences in trial design.
*Response defined as ≥30% improvement in CMAI total score and Patient Global Impression of Change score improvements ≤3 lasting ≥4 consecutive weeks.
AAD, agitation in Alzheimer's dementia; AXS-05, dextromethorphan-bupropion; Brex, brexpiprazole; BL, baseline; CMAI, Cohen-Mansfield Agitation Inventory; DB, double blind; DBP, DB period; OLP, open label period; Pbo, placebo; Wk, week.

1. FDA. Brex PI. Available at: https://bit.ly/4gbbKLg (accessed 5 October 2024); 2. FDA. News release, 11 May 2023. Available at: https://bit.ly/3zode4k (accessed 5 October 2024); 3. Lee D, et al. *JAMA Neurol*. 2023;80:1307–16; 4. Cummings J, et al. *Neurology*. 2024;102(17 Suppl. 1):PL5.004; 5. Herrmann N, et al. *Am J Geriatr Psychiatry*. 2019;27:1161–73; 6. ClinicalTrials.gov. NCT04516057. Available at: https://bit.ly/4gbcSPa (accessed 5 October 2024).

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# Safety: New and emerging therapies for AAD

| | Approved (FDA 2023)[†1,2] | Under investigation | |
|---|---|---|---|
| **Agent** | **Brexpiprazole (phase III)[3]** | **AXS-05 (phase III)[4]** | **Nabilone (phase II)[6]** |
| **Patients** | N=345 (Brex: n=228; Pbo: n=114) | OLP: N=178<br>DBP: n=108 responders*<br>(AXS-05: n=53; Pbo: n=55) | N=38 |
| **TEAEs** | Brex, 41%; Pbo, 31%<br>**Discontinuations**:<br>Brex, 5%; Pbo, 4% | AXS-05, 28%; Pbo, 22%<br>**Discontinuations**:<br>AXS-05, 0%; Pbo, 2% | Significantly more vs Pbo during the nabilone phase (p=0.05) |
| **Key TEAEs (≥5% in Tx arm)** | Headache (Brex: 7%; Pbo: 7%) | Diarrhoea (AXS-05: 8%; Pbo: 4%), fall (AXS-05: 8%; Pbo: 4%) and back pain (AXS-05: 6%; Pbo: 4%)[5] | Sedation (Nabilone: 45%; Pbo: 16%), treatment-limiting sedation (Nabilone: 13%; Pbo: 3%) and falls (Nabilone: 21%; Pbo: 18%) |

*Response defined as ≥30% improvement in CMAI total score and Patient Global Impression of Change score improvements ≤3 lasting ≥4 consecutive weeks.
†Brex has a block box warning for an increased mortality risk in elderly patients with dementia-related psychosis and an increased risk of suicidal thoughts and behaviours in paediatric patients and young adults using antidepressant therapy. Direct comparisons between trials should not be made due to differences in trial design.
AAD, agitation in Alzheimer's dementia; AXS-05, dextromethorphan-bupropion; Brex, brexpiprazole; DBP, double blind period; NPS, neuropsychiatric symptoms; OLP, open label period; Pbo, placebo; TEAE, treatment-emergent adverse event; Tx, treatment.
1. FDA. Brex PI. Available at: https://bit.ly/4gbbKLg (accessed 5 October 2024); 2. FDA. News release, 11 May 2023. Available at: https://bit.ly/3zode4k (accessed 5 October 2024); 3. Lee D, et al. *JAMA Neurol*. 2023;80:1307–16; 4. Cummings J, et al. *Neurology*. 2024;102(17 Suppl. 1):PL5.004; 5. Cummings J, et al. Poster presented at: ASCP 2024, 28–31 May 2024, Miami, FL, USA; 6. Herrmann N, et al. *Am J Geriatr Psychiatry*. 2019;27:1161–73.

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