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

Practice aid for supporting the pharmacological management of agitation in Alzheimer's dementia

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The IPA approach to managing people living with AAD[1]

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**

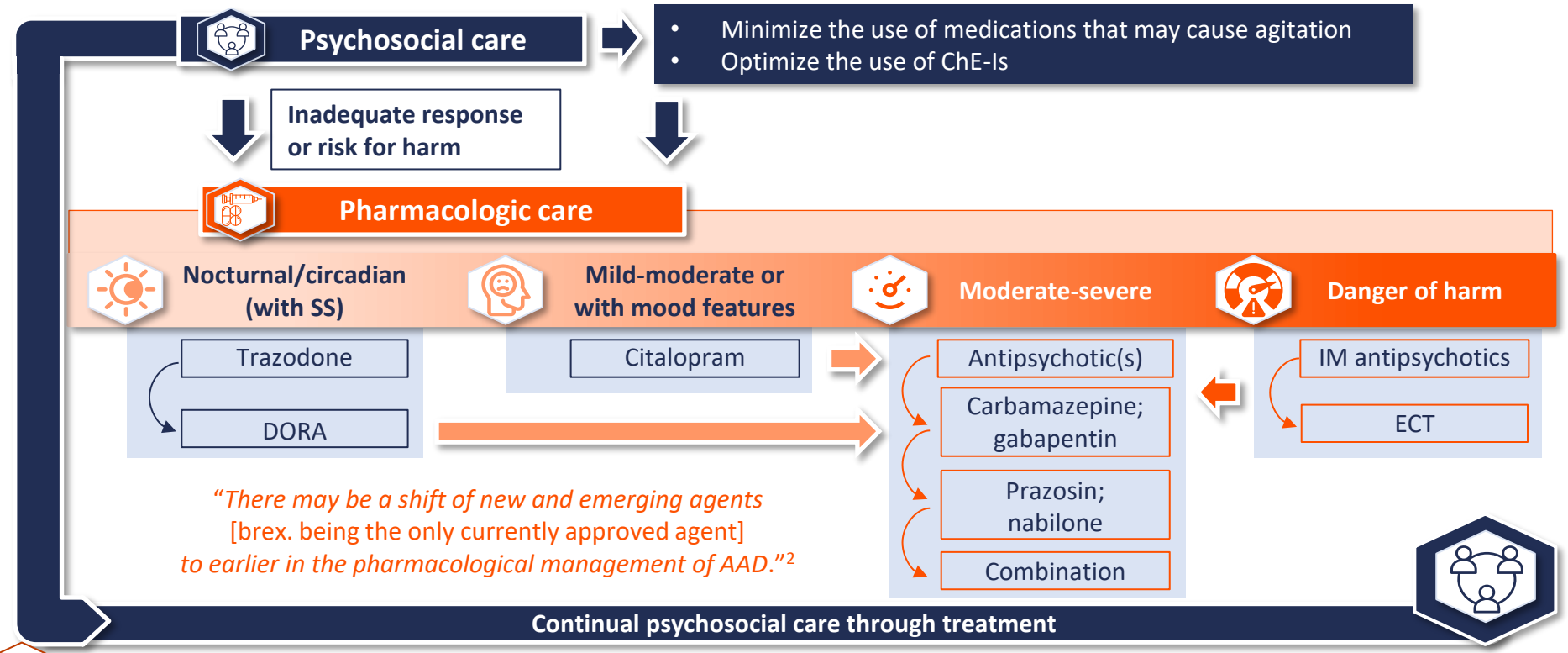
Post-intervention

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

What the experts say about patient care and agitation management[2]

Before the onset of agitation	Understanding the behaviours	Psychosocial care
"Defence is the best offense"	**"It has to be agitation"**	**"We always do psychosocial care"**
• Is this patient at risk for developing these behaviours? • Have a plan in place before the behaviours begin	• Rule out other potential underlying causes like acute infection or delirium • Look at recent medication changes • Look for drug–drug interactions	• Before, during and after treatment with a pharmacologic agent • If the psychosocial intervention is not sufficient, or there's immediate risk of harm, then we choose a pharmacologic intervention

Current approach to pharmacological management[1]



What the experts say about managing patients when treating with pharmacological agents[2]

Selecting treatment

"You'll want to look at:

- The history of response and the history of side effects
- The severity of agitation
- The severity of cognitive impairment (one of the predictors of response)
- The concomitant neuropsychiatric symptoms (what do you want [to achieve]? e.g. sedation)"

Monitoring

- "If we collect data before [we treat], we will have a better sense of risk: how behaviours are changing; how much distress they are causing"
- "We can then monitor whether those things are changing at least 3 months later, and certainly every 6 months"

Treatment switching

- "Switching treatments is recommended, usually around 8 weeks or after 2 months"

Efficacy and safety of new and emerging therapies for AAD

	Approved (FDA 2023)[2,4]	Under investigation	
Agent	**Brex (phase III)[5]**	**AXS-05 (phase III)[6]**	**Nabilone**
MoA	• NMDA receptor antagonist • Sigma-1 receptor agonist	• Noradrenergic α_{1B} and α_{2C} and 5-HT_{2A} receptor antagonist • Serotonin 5-HT_{1A} and dopamine D2 receptor partial agonist	• CB1 and CB2 partial agonist
Impact	• Influences mood and behaviour through modulation of NMDA receptors and stimulation of the dopaminergic system	• Suppression of multiple receptors related to agitation, aggression, impulsiveness, arousal and psychosis	• Increased serotonergic signalling • Neuroprotection through reduced oxidative stress, reduced TNF-α, and reduced glutamate release • Improved circadian rhythm
Patients	N=345 (Brex: n=228; Pbo: n=114)	OLP: N=178 DBP: n=108 responders* (AXS-05: n=53; Pbo: n=55)	Phase II[8] N=38 (DB crossover)
			Phase III[9] **NCT04516057** N=112; 16 weeks (Nabilone vs Pbo)
Primary endpoint	**Mean ΔCMAI (BL–Wk 12)**: Brex: -22.6; Pbo: -17.3 Cohen's *d* effect size: 0.35 (p=0.003)	**OLP**: Improvement in CMAI (Wk 1–Wk 5, p<0.001) **DBP**: Substantial delay in time to relapse vs Pbo (p=0.014)	**Estimated ΔCMAI**: Cohen's *d* effect size: 0.52
			Primary endpoint: ΔCMAI (BL–Wk 8) **Estimated completion**: October 2025
TEAEs	Brex, 41%; Pbo, 31% Discontinuations: Brex, 5%; Pbo, 4%	AXS-05, 28%; Pbo, 22% **Discontinuations**: 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%)[7]	Sedation (Nabilone: 45%; Pbo: 16%), treatment-limiting sedation (Nabilone: 13%; Pbo: 3%) and falls (Nabilone: 21%; Pbo: 18%)

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.

Abbreviations and references

Abbreviations

5-HT, serotonin receptors; AAD, agitation in Alzheimer's dementia; AXS-05, dextromethorphan-bupropion; Brex, brexpiprazole; BL, baseline; CB1/2, cannabinoid receptor type 1/2; CHE-I, cholinesterase inhibitor; CMAI, Cohen-Mansfield Agitation Inventory; D2, dopamine receptor type 2; DB, double blind; DBP, DB period; DORA, dual orexin receptor antagonist; ECT, electroconvulsive therapy; FDA, US Food and Drug Administration; IM, intramuscular; IPA, International Psychogeriatric Association; MDT, multidisciplinary team; MoA, mechanism of action; NMDA, N-methyl-d-aspartate; NPS, neuropsychiatric symptoms; OLP, open label period; Pbo, placebo; SS, sundown syndrome; TEAE, treatment emergent adverse event; TNF, tumour necrosis factor; Tx, treatment; Wk, week.

References

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