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AAD Treatment Guidelines: Addressing Challenges & Unmet Needs

ReachMD Announcer:
Welcome to ReachMD.
This medical industry feature, titled "AAD Treatment Guidelines: Addressing Challenges & Unmet Needs" is the third episode in a three-part series sponsored by Otsuka and Lundbeck.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host Dr. Jennifer Caudle. And joining me to walk us through some of the treatment guidelines for agitation in Alzheimer's dementia is Dr. David Sultzer. Dr. Sultzer is professor of psychiatry and human behavior at UC Irvine in California.

Dr. Sultzer, welcome to the program.

Dr. Sultzer:
Thanks so much for having me. It's a pleasure to be here.

Dr. Caudle:
Dr. Sultzer, let's begin with an overview of agitation in Alzheimer's dementia, or AAD for short. Can you tell us about both its prevalence and defining behaviors?

Dr. Sultzer:
When we look at agitation in Alzheimer's disease, we find that it's fairly prevalent in patients with Alzheimer's dementia even across different patient settings.

Agitation is a common neuropsychiatric symptom that is also observed across different Alzheimer's severity levels.

Now the International Psychogeriatric Association, also known as the IPA, has developed a provisional consensus definition for agitation in cognitive disorders that requires patients to meet four specific criteria.

The IPA also defines three agitation behavior domains that are associated with emotional distress, including excessive motor activity, verbal aggression, and physical aggression.[4]

Dr. Caudle:
Now with that background laid out for us, what can you tell us about the pathophysiology of AAD as we understand it?

Dr. Sultzer:
Sure. From the available literature, agitation may be related to an imbalance of the top-down executive control and the bottom-up emotional drive processes that regulate emotion.[5]

In agitation in Alzheimer's disease, we see neurodegeneration from tau pathology in the prefrontal cortex and subcortical regions, including the amygdala.6-9 The prefrontal cortex plays a key role in executive control over emotion and behavior, while the amygdala is a key mediator of emotional drive.[10,11]

Dysfunction in the monoamine neurotransmitter systems of norepinephrine, serotonin, and dopamine, or NSD for short, can disrupt the signal pathways in these regions and lead to agitation.[12]

Dr. Caudle:
And now with these considerations in mind, what types of interventions are available to treat patients with AAD?

Dr. Caudle:
For those just tuning in, you're listening to ReachMD.
I'm Dr. Jennifer Caudle and today I'm speaking with Dr. David Sultzer about treatment guidelines for agitation in Alzheimer's dementia.

Dr. Sultzer:
We first need to start with a differential diagnosis to carefully evaluate and treat general medical, psychiatric, environmental, or psychosocial problems that may be triggering the disturbance.[13]

Often a first line approach to treatment includes nonpharmacological approaches like behavioral management interventions, emotion-based therapies and/or stimulation-based treatments such as music or pet therapies.[13] These strategies usually include considerable engagement with caregivers.

But if nonpharmacological interventions don't work or there are more urgent or safety concerns, then we should consider adding medication to the overall treatment plan. In this case, the APA and the Harvard South Shore Program both recommend antipsychotics for agitation in dementia.[13,14]

Dr. Caudle:
Now we just discussed interventions to treat AAD, but as I understand it, there still may be some core issues clinicians are dealing with. Can you describe those for us?

Dr. Sultzer:
Sure. So despite the guidelines recommending antipsychotics to help treat agitation in Alzheimer's disease, there are currently no FDA-approved pharmacological treatments for AAD.[14]

And the efficacy and safety profiles for second-generation antipsychotics for behavioral symptoms can vary based on receptor binding profiles.[15]

In addition to antipsychotics, clinicians often prescribe antidepressants, anxiolytics, sedative hypnotics, or other medications to control behavioral symptoms, but they do so off label.[16,17]

And these treatment options are only modestly effective, and controlled trials often don't support their benefit. They also have relatively poor safety and tolerability profiles.[16,17]

Dr. Caudle:
And now you mentioned these agents are prescribed off label. Can you elaborate a bit on the risk/benefit profiles for patients taking these medications?

Dr. Sultzer:
These treatments can also be associated with adverse events such as sedation, orthostatic hypotension, falls, extrapyramidal symptoms, cognitive slowing, and cerebrovascular and cardiovascular complications.[17,24-26]

Now benzodiazepines have been shown to be modestly beneficial in cases for treating agitation in Alzheimer's Disease, but they are occasionally prescribed for patients with prominent anxiety.27 And we have some safety concerns when they're used to manage agitation in the elderly, specifically due to the risk of cognitive impairment, fractures, and falls.[28]

We also sometimes prescribe antidepressants for agitation and aggression in dementia, but there's currently limited evidence to support its use here.[29,30] While they're tolerated reasonably well, we need more evidence to know if they really are safe and effective treatments for agitation in Alzheimer's disease.[30]

Dr. Caudle:
Now we're almost out of time, but before we close, do you have any key takeaways you'd like to share with our audience today?

Dr. Sultzer:
Yes, while current guidelines recommend tailoring a comprehensive treatment plan with nonpharmacological and medication interventions as needed for AAD,[13,14] there's currently no FDA-approved treatment for agitation in Alzheimer's Disease.[14]

And even when we prescribe them off label, they're associated with mixed risk-to-benefit profiles.[16,17]

So we really need approved pharmaceutical treatment options with demonstrated efficacy and safety for the treatment of agitation in Alzheimer's Disease that ideally address the specific pathophysiology of agitation in Alzheimer's dementia.[24]

Dr. Caudle:
Thank you, those are great practical takeaways to take into consideration as we end today's program. I'd like to thank my guest, Dr. Sultzer, for helping us better understand unmet needs in AAD treatment.

Dr. Sultzer, it was great speaking with you today.

Dr. Sultzer:
It was a pleasure to be here. Thank you.

ReachMD Announcer:
This program was sponsored by Otsuka and Lundbeck. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

References:

1. Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. Alzheimers Dement. 2022;18. doi:10.1002/alz.12638. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed April 14, 2022.
2. Fillit H, Aigbogun MS, Gagnon-Sanschagrin P, et al. Impact of agitation in long-term care residents with dementia in the United States. *Int J Geriatr Psychiatry.* 2021;36(12):1959-1969. doi:10.1002/gps.5604
3. Halpern R, Seare J, Tong J, et al. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. *Int J Geriatr Psychiatry.* 2019;34(3):420-431. doi:10.1002/gps.5030
4. Cummings J, Mintzer J, Brodaty H, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. I*nt Psychogeriatr*. 2015;27(1):7-17. doi:10.1017/S1041610214001963
5. Rosenberg PB, Nowrangi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer's disease: what might be associated brain circuits? *Mol Aspects Med.* 2015;43-44:25-37. doi:10.1016/j.mam.2015.05.005
6. Tekin S, Mega MS, Masterman DM, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Ann Neurol*. 2001;49(3):355-361. doi:10.1002/ana.72
7. Guadagna S, Esiri MM, Williams RJ, et al. Tau phosphorylation in human brain: relationship to behavioral disturbance in dementia. *Neurobiol Aging*. 2012;33(12):2798-2806. doi:10.1016/j.neurobiolaging.2012.01.015
8. Hu X, Meiberth D, Newport B, et al. Anatomical correlates of the neuropsychiatric symptoms in Alzheimer's disease. *Curr Alzheimer Res*. 2015;12(3):266-277. doi:10.2174/1567205012666150302154914
9. Trzepacz PT, Yu P, Bhamidipati PK, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement*. 2013;9(5 Suppl):S95-S104.e1. doi:10.1016/j.jalz.2012.10.005
10. Salzman CD, Fusi S. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex.*Annu Rev Neurosci*. 2010;33:173-202. doi:10.1146/annurev.neuro.051508.135256
11. Arnsten AF, Raskind MA, Taylor FB, Connor DF. The effects of stress exposure on prefrontal cortex: translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiol Stress.* 2015;1:89-99. doi:10.1016/j.ynstr.2014.10.002
12. Miller CWT, Hodzic V, Weintraub E. Current understanding of the neurobiology of agitation. *West J Emerg Med* 2020;21(4):841-848. doi:10.5811/westjem.2020.4.45779
13. Reus, V. I., Fochtmann, L. J., Eyler, A. E., et al (2016).*The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia.* 1st Edition. American Psychiatric Association. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890426807
14. Chen, A., Copeli, F., Metzger, E., Cloutier, A., & Osser, D. N. (2021). The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An update on management of behavioral and psychological symptoms in dementia. Psychiatry Research, 295, 113641. doi:10.1016/j.psychres.2020.113641.
15. Ma, H., Huang, Y., Cong, Z., et al (2014). The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. *Journal of Alzheimer's disease*, 42(3), 915-937.

doi:10.3233/JAD-140579.
16. Aigbogun, M. S., Cloutier, M., Gauthier-Loiselle, M., et al (2020). Real-World Treatment Patterns and Characteristics Among Patients with Agitation and Dementia in the United States: Findings from a Large, Observational, Retrospective Chart Review. *Journal of Alzheimer's Disease*, 77(3), 1181-1194. doi:10.3233/jad-200127.
17. 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.
18. Janssen Pharmaceuticals, Inc. Risperdal (risperidone) [package insert]. 2022.
19. AstraZeneca Pharmaceuticals LP. Seroquel (quetiapine) [package insert]. 2022.
20. Eli Lilly and Company. Zyprexa (olanzapine) [package insert]. 2021.
21. Otsuka America Pharmaceutical, Inc. Abilify (aripiprazole) [package insert]. 2020.
22. 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.
23. Schneider, L. S., Dagerman, K. S., & Insel, P. (2005). Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*, 294(15), 1934-1943. doi:10.1001/jama.294.15.1934.
24. Caraci, F., Santagati, M., Caruso, G., et al (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.
25. 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.
26. 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.
27. Rabins, P. V., Blacker, D., Rovner, B. W., Rummans, T., Schneider, L. S., Tariot, P. N., . . . Fochtmann, L. J. (2007). American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. The American Journal of Psychiatry, 164(12 Suppl), 5-56.
28. Defrancesco, M., Marksteiner, J., Fleischhacker, W. W., et al. (2015). Use of Benzodiazepines in Alzheimer's Disease: A Systematic Review of Literature. *The International Journal of Neuropsychopharmacology*, 18(10), pyv055. doi:10.1093/ijnp/pyv055.
29. Porsteinsson, A. P., Drye, L. T., Pollock, B. G., et al (2014). Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*, 311(7), 682-691.doi:10.1001/jama.2014.93.
30. Seitz, D. P., Adunuri, N., Gill, S. S., et al (2011). Antidepressants for agitation and psychosis in dementia.*Cochrane Database Systematic Reviews* (2), Cd008191. doi:10.1002/14651858.CD008191.pub2.

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