American Academy of Physician Associates

Pharmacologic Approaches in the Management of Neuropsychiatric Symptoms (NPS) in Alzheimer's Disease (AD)

Overview

- Up to 98% of patients with Alzheimer's disease (AD) have at least one neuropsychiatric symptom (NPS).
    - Primary NPS: Aggression, agitation, apathy, anxiety, depression, psychosis (delusions or hallucinations)
    - Additional NPS: Sleep disorders/nighttime behaviors, appetite/eating problems, disinhibition, and/or motor disturbances
- ~90% of older adults regularly take ≥1 prescription drug, 80% take ≥2 prescription drugs, and **36% regularly take at least 5 different prescription drugs**.
    - Rates do **not** include use of supplements or other OTC agents.
- Most national organizations (AAGP, AGS, APA, NICE, and Alzheimer's Association) recommend the **judicious use** of pharmacologic options when nonpharmacologic interventions have not been sufficiently successful in addressing NPS in AD:
    - If patient presents as a significant risk of harm to self or others owing to aggression or psychosis
    - If patient is severely distressed
    - If patient has major depression with or without suicidal ideation[1]
- Many common medications are inappropriate for older patients or patients with AD.
    - Some may contribute to the appearance or severity of NPS.
    - Some agents used to manage symptoms associated with NPS (e.g. agitation, depression, anxiety) are **not** indicated or are **contraindicated** for use in older patients with dementia:
        - Antipsychotics
        - Benzodiazepines
        - Antidepressants
- General recommendations for use of medications in this population (outside of ED):
    - Use all medication with caution and closely monitor.
    - Initiate at lowest dose and slowly titrate up to minimum effective dose.
    - Repeatedly assess whether medication is of continued benefit and/or if there have been any reported adverse drug reactions (ADRs).[1]
    - Carefully consider risk of drug-drug interactions given likelihood of polypharmacy.

Current FDA-Approved Medications for Alzheimer's Disease

- Symptomatic medications:
  - The cholinesterase inhibitors donepezil (Aricept; mild, moderate, severe AD), galantamine (Razadyne, Reminyl; moderate-to-severe AD), rivastigmine (Exelon; moderate to severe AD)
  - Oral NMDA (N-methyl-D-aspartate) blocker memantine (Namenda)
- Medications to slow disease progression in patients with MCI due to AD and mild AD dementia:
  - Lecanemab (Leqembi)
  - Donanemab (Kisunla)

Current Medications to Mitigate or Manage NPS in Patients with AD[2]

Overview

- Specific medications can be used (optimally for short durations) for various NPS.
- Note: ***many medications have an FDA boxed warning against their use in elderly patients with dementia***.
  - Recognize that many patients, their care partners* or children often search the medication online and will identify any risks and warnings.
  - This recommendation is particularly important regarding antipsychotic medications that are FDA-approved for the NPS but have boxed warnings.
  - This is also true of antipsychotic medications that are otherwise FDA-approved but are being used off-label for patients with AD.
  - It is important to **acknowledge these risks and warnings up front** with the patient/care partner in order to put them into context.
  - Be ready to answer all questions and address any concerns regarding the warnings, even before discussing the potential benefits of the medications.
- Each NPS has unique pharmacologic agents that can be considered and prescribed if necessary.
- Before prescribing anything for this population:
  - First ensure an accurate diagnosis of the NPS.
  - Review the patient's current list of **all** other medications (and OTC agents).
  - Identify any other medical conditions, allergies, or intolerances that may affect medication selection, effectiveness, and safety.
  - Provide extensive education to the patient and care partner about benefits and risks.

SLEEP

- There have been inconsistent results among the numerous studies on improving sleep disorders in elderly patients with AD/dementia.
- There are both prescription and OTC agents used by patients for sleep disorders.

- **<u>All</u> sleep-inducing agents carry an increased risk of falling and confusion among older patients**.
- The only **prescription agents** currently indicated for management of insomnia in AD are suvorexant (Belsomra), a dual orexin receptor antagonist,[2,3] and daridorexant (Quviviq), an orexin receptor antagonist.
    - Off-label agents include:
        - Some antidepressants: bupropion (Aplenzin), venlafaxine (Effexor), and the tricyclic antidepressant nortriptyline (Pamelor)
        - Benzodiazepines (which are generally contraindicated in older patients with dementia)
        - Antipsychotic agents: risperidone (Risperdal), quetiapine (Seroquel), and olanzapine(Zyprexa) (all of which are not generally recommended for elderly dementia patients)
        - Studies also haven't demonstrated any consistent (90%) benefit with trazodone (Deyrel, Oleptro) or ramelteon (Rozerem).[3]
- Donepezil (Aricept) is traditionally prescribed for patients with Alzheimer's disease, but may cause insomnia.
- OTC: Melatonin and other OTC sleep aids
    - There is questionable efficacy of melatonin.[1]
    - Melatonin has potential adverse effects, including dizziness, confusion, headaches, gastrointestinal complaints, hypotension, and cognitive impairment.
    - Inform patients and their care partners that even though melatonin is sold OTC, it is not a benign sleep aid option.
    - Other sleep aids: diphenhydramine (DIPH; Benadryl) or doxylamine (DOX)[4]
        - Sleep aids containing DIPH or DOX have important risks when used in elderly patients.
        - Deemed potentially inappropriate and unsafe by Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
        - Increased risk of anticholinergic effects, dizziness, cognitive impairments
        - Increased risk of falling from drowsiness, dizziness, confusion
        - May increase risk of hepatic/renal insufficiency
        - Risk of drug interactions with other prescription medications
        - DIPH or DOX should not automatically be considered "safe" for use in this population.

APATHY

- One of the first and most common NPS in patients with Alzheimer's disease
    - Manifests as a lack of motivation, loss or interest in recreational activities, lack of initiative to participate in daily tasks
    - Patients may withdraw from social interactions and appear indifferent to the world around them.
- There are no specific medications to manage apathy.
- Agents that have shown some benefit in reducing apathy include:

    - Cholinesterase inhibitors typically prescribed for AD, including donepezil galantamine, and rivastigmine
    - The psychostimulant methylphenidate (Ritalin)
    - Some antidepressants may improve while others may worsen apathy.
        - It can be difficult to know how a patient will respond.
- There has been research on the use of transcranial magnetic stimulation (TMS) in combination with cognitive training.
    - Benefits can persist for at least 6 months after treatment.[5]

DEPRESSION

- Common NPS that may also precede the diagnosis of AD.
- Occurs in at least 20% of patients with dementia[1] and may worsen cognitive complaints.
- Some antidepressants can ameliorate depressive symptoms and improve quality of life—**but** worsen cognition.
    - Very few RCTs on the efficacy of antidepressants in AD
    - Many studies have found minimal significant difference between the antidepressant vs. placebo.[6]
- Recommendations to avoid tricyclic antidepressants (TCAs) and agents with significant anticholinergic effects.[1]
- Minimal evidence demonstrating the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) to manage cognition and depression of AD patients[7]
- Nevertheless, the SSRIs sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa) and escitalopram (Lexapro) are most often used (OFF-LABEL) for depression in patients with AD.

ANXIETY, AGITATION, AND AGGRESSION

- ***Anxiety*** and ***agitation*** can sometimes be difficult to distinguish from one another.
    - Agitation can manifest with verbal outbursts, intense anxiety, physical outbursts (aggression), crying, and aimless wandering.
    - Unchecked, agitation can lead to verbal and/or physical aggression**.**
    - **≥** 20% of patients with AD experience agitation at some point in the disease process.
    - Nonpharmacologic interventions may afford some benefit.
    - Eventually they become ineffective, requiring pharmacologic interventions.
- Historically, antidepressants and benzodiazepines have been used (**off-label**) to manage anxiety and antipsychotics have been used to address agitation and aggression.
    - Significant risks associated with many of these agents.
    - Ongoing questions regarding whether the use of benzodiazepines (BZDs) may facilitate development of AD
    - Evidence suggests BZDs impair cognitive function and facilitate falls in elderly people.[1]

    - Despite an apparent high reliance on BZDs (especially in long-term care facilities), there is a paucity of evidence supporting their benefit.[8]
- Antidepressants (off-label)
    - Citalopram (Celexa) has been used to manage agitation/anxiety and depression.
        - Associated with impaired cognition and adverse cardiac effects including QTc prolongation[1]
        - Limit daily dose to ≤20 mg and use it only for patients with moderate agitation and minimal cognitive impairment to reduce risks[1]
    - Escitalopram (Lexapro) as an appropriate alternative to citalopram
        - Lower risk of QT prolongation at therapeutic levels[9]
    - Mirtazapine (Remeron) found to be comparable to placebo
        - Potentially higher risk of mortality[10]
- Antipsychotics (off-label) as standard treatment
    - The majority of patients in nursing homes and up to 1 in 3 community-dwelling elderly patients are prescribed psychotropic medications.
    - Agents may afford modest benefits in ameliorating aggressive behaviors.
    - Associated with substantial risks including increased mortality[1]
        - The increased risk of cerebrovascular events in elderly patients with dementia was first identified in the early 2000s, followed by evidence of an increased risk of death.
        - In 2008, the FDA has placed a black box warning on **all antipsychotics,** noting these drugs are not approved for treating dementia-related psychosis and that they can increase the risk of death.
        - In absence of alternative, continue to be used **off-label**
    - Recent Cochrane report concluded there is uncertainty as to whether typical (first generation) antipsychotics (FGAs, e.g. haloperidol [Haldol decanoate] and thiothixene [Navane]), improve agitation
        - May slightly improve psychosis
        - Associated with somnolence
        - Increased risk of extrapyramidal symptoms (EPS)
    - Atypical (second generation) agents (SGAs) slightly reduce agitation with a negligible effect on psychosis.
        - Slightly increased risk of EPS, serious adverse events (AEs), and death
        - Increased risk of somnolence[11]
        - Risperidone (Risperdal)
            - Increased risk for cerebrovascular AEs and death[12]
        - Olanzapine (Zyprexa)
            - Increased risk for profound restlessness, hallucinations, loss of visual acuity and dizziness, increased risk for falls[13]
        - Aripiprazole (Abilify**)**
            - Increased risk for morbidity due to cardiovascular or infectious (pneumonia) causes
        - Quetiapine (Seroquel)

        - Associated with significantly greater cognitive decline vs. placebo[14]
    - Brexpiprazole (Rexulti), an oral atypical antipsychotic, is the first agent to receive FDA approval for the management of agitation in AD even though it **carries the boxed warning**.
        - AEs: dizziness, high blood sugar, insomnia, somnolence, urinary tract infections, headaches, and cerebrovascular events
        - Patients must be closely monitored while taking this medication.[15,16]
        - "Maintenance" medication—should not be used "PRN" for breakthrough agitation
        - Dose adjustments may be required for patients based on their other medications or on renal/hepatic function.[15]
    - Other agents under investigation for this indication include escitalopram (Lexapro) and dextromethorphan-bupropion (Auvelity).[16]

PSYCHOSIS (DELUSIONS AND HALLUCINATIONS)

- There is currently **no agent** approved for the management of psychotic symptoms, including delusion and hallucinations, for elderly patients with AD.
- The 2016 APA guidelines recommend that use of non-emergency antipsychotic agents for treatment of psychosis should be **limited to those patients with severe or dangerous symptoms or symptoms that cause significant distress to the patient (or care partner) after objective discussions about the risks and benefits**.[17]
    - Antipsychotics are used **off-label** despite their boxed warning.
- The atypical antipsychotic pimavanserin (Nuplazid) is approved for management of hallucinations and delusions in **Parkinson's disease psychosis**,
    - Used off-label for psychosis in AD.
    - Has potentially serious adverse effects:
        - Nausea, peripheral edema, confusion, hallucinations
        - Increased risk of mortality
- Brexpiprazole (Rexulti) is approved for management of agitation in AD, but **not** approved for management of psychosis.
- Brexpiprazole, pimavanserin, and other SGAs are often considered for short-duration **off-label** use under close monitoring when absolutely necessary.
- When prescribing these agents, it is recommended to initiate with low doses, titrate slowly to the lowest effective dose, and use for the shortest duration possible.

*care partner: We have chosen to use the term "care partner" because it implies a more collaborative and intimate relationship between the patient receiving the care and the person(s) providing the care. It refers to the person who either lives with the patient or sees them ≥1-2X/week and is a more inclusive term than "caregiver."

References

1. Phan SV, Osae S, Morgan JC, Inyang M, Fagan SC. Neuropsychiatric symptoms in dementia: considerations for pharmacotherapy in the USA. Drugs in R&D.2019;19:93-115.
2. Varadharajan A, Davis AD, Ghosh A, et al. Guidelines for pharmacotherapy in Alzheimer's disease -a primer on FDA-approved drugs. J Neurosci Rural Pract. 2023;14(4):566-573.
3. McCleery J, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD009178.
4. Abraham O, Schleiden L, Albert SM. Over-the-counter medications containing diphenhydramine and doxylamine used by older adults to improve sleep. Int J Clin Pharm. 2017;39:808-817.
5. Nguyen J-P, Suarez A, Kemoun G, et al. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. Neurophysiol Clin. 2017;47(1):47-53.
6. Orgeta V, Tabet N, Nilforooshan R, Howard R. Efficacy of antidepressants for depression in Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis. 2017;58(3):725-733.
7. Qin M, Wu J, Zhou O, Liang Z, Su Y. Global cognitive effects of second-generation antidepressants in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. J Psychiatr Res. 2022;155:371-379.
8. Defrancesco M, Marksteiner J, Fleischhacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: a systematic review of literature. Int J Neuropsychopharmacol. 2015;18(10):pyv055.
9. Takemoto M, Ohta Y, Hishikawa N, et al. The Efficacy of Sertraline, Escitalopram, and Nicergoline in the Treatment of Depression and Apathy in Alzheimer's Disease: The Okayama Depression and Apathy Project (ODAP). J Alzheimers Dis. 2020;76(2):769-772.
10. Banerjee S, High J, Stirling S, et al. Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomized, double-bind, placebo-controlled trial. Lancet. 2021;398:1487-1497.
11. Mühlbauer V, Möhler R, Dichter MN, et al. Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2021;12(12):CD013304.
12. Yunusa I, El Helou ML. The use of risperidone in behavioral and psychological symptoms of dementia: a review of pharmacology, clinical evidence, regulatory approvals, and off-label use. Front Pharmacol. 2020;11:598.
13. Coles M. Caution with olanzapine use in dementia. Aust Prescr. 2021;44:40.
14. Ballard C, Margallo-Lana M, Juszczak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomized double blind placebo controlled trial. BMJ. 2005;330(7496):874.

15. Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurol. 2023;80(12):1307-1316.
16. Lee D, Clark ED, Antonsdottir IM, Porsteinsson AP. Brexpiprazole for agitation associated with dementia due to Alzheimer's disease. J Am Med Dir Assoc. 2024;25(10):105173.
17. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. Am J Psychiatry 173:5, May 2016 ajp.psychiatryonline.org 543-546.