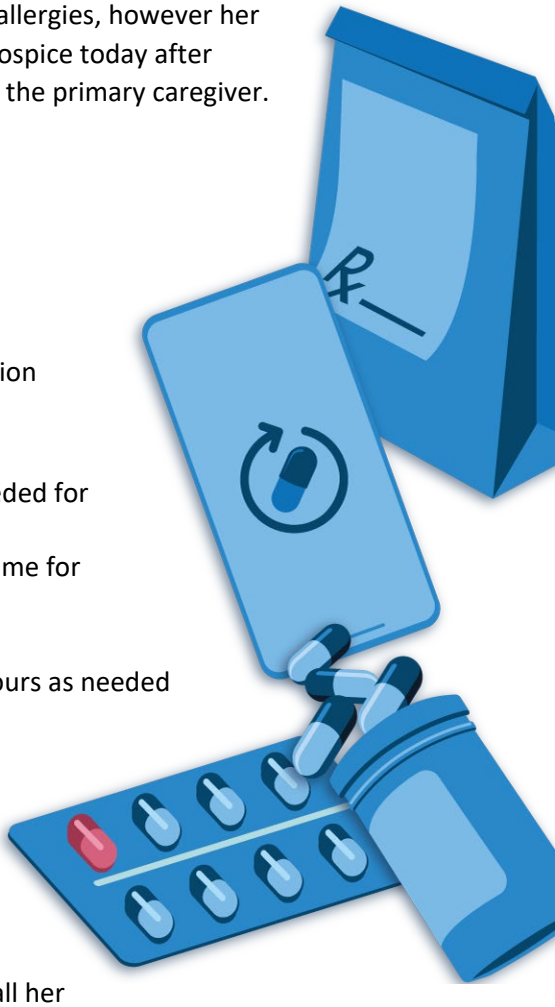
PALLIATIVE PEARLS
BY ENCLARA PHARMACIA

Dementia Medications & Deprescribing: A Revision
February 2023

This month, we revisit a popular Palliative Pearls case published in April 2017. We have incorporated guidance from recently published literature along with revisions for your enrichment.

PATIENT CASE

MJ is an 86-year-old female with a primary diagnosis of Alzheimer's disease and history of depression, Type II DM, HTN, TIA and osteoarthritis. Amoxicillin and sulfa are listed as allergies, however her reaction to these medications is not documented. MJ was readmitted to hospice today after being off service for 8 months. She lives at home with her daughter who is the primary caregiver.



CURRENT MEDICATIONS

- Acetaminophen 1000mg PO three times daily for pain
- Acetaminophen 650mg PR every 4 hours for mild pain or fever
- Aspirin 81mg chewable by mouth daily for clot prevention
- Bisacodyl 10mg PR daily as needed for constipation
- Calcium w/ Vit D 600mg-400units PO twice daily for supplementation
- Donepezil (Aricept®) 10mg PO daily for memory
- Escitalopram (Lexapro®) 20mg PO daily for depression
- Haloperidol 2mg/mL concentrate – 0.5mg PO every 6 hours as needed for agitation
- Insulin glargine (Lantus®) inject 9 units sub cut every night at bedtime for diabetes
- Lidocaine 5% patch – Apply 2 patches daily to painful area
- Lorazepam 0.5mg PO every morning and afternoon and every 2 hours as needed for anxiety
- Melatonin 10mg PO every night at bedtime as needed for sleep
- Memantine (Namenda®) 10mg PO twice daily for memory
- Polyethylene glycol (Miralax®) powder 17gm PO daily for constipation
- Valsartan-HCTZ 160mg-25mg PO daily for the blood pressure

The pharmacist reviewing the readmission notes that MJ has been taking all her medications prior to readmission and tolerating them without known side effects. Currently, MJ has no unresolved signs or symptoms, including pain. The pharmacist recommends discontinuation of the calcium supplement, Aricept® and Namenda® and advises the nurse case manager of the daily maximum

limit for acetaminophen. The nurse will discuss these recommendations with the hospice team but notes it will be difficult to stop the Aricept® and Namenda® because the patient's family is "not ready for this". She also notes that MJ's family is interested in learning more about Nuedexta® for agitation. What information can the pharmacist provide to support the nurse in having deprescribing discussions with the hospice team and caregiver and to guide her on the use of Nuedexta® in Alzheimer's disease?

ARICEPT® AND NAMENDA® IN PATIENTS WITH ALZHEIMER'S DISEASE

Alzheimer's disease is the most common form of dementia in the elderly affecting memory, thinking, and behavior. It is characterized by plaques, tangles, and decreased acetylcholine in the brain. Two drug classes are indicated for the treatment of dementia associated with Alzheimer's disease: (1) Cholinesterase inhibitors (ChEIs) (e.g., donepezil (Aricept®), galantamine (Razadyne®), and rivastigmine (Exelon®) and (2) the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Namenda®). Namzaric® is an extended-release form containing both donepezil and memantine and Adlarity® is a weekly transdermal patch containing donepezil. [1,2]

The ChEIs inhibit acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine, thereby improving the availability of acetylcholine in the brain. Memantine works by slowing intracellular calcium accumulation and helps to prevent further nerve damage, which is thought to prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. [1,2]

SUPPORTING LITERATURE FOR USE OF DEMENTIA MEDICATIONS IN PATIENTS ON HOSPICE

Evaluation of randomized controlled trials (RCTs) suggest that donepezil and memantine lead to some improvements in patients' global cognition, functional communication, and some behavioral symptoms (agitation and aggression) in patients with moderate to severe dementia.[3]

The effectiveness of donepezil is less evident when patients reach a severe stage of dementia when cognitive and functional abilities and social interactions are very limited. Along with some benefit in behavioral symptoms, reports of cognitive and global benefits of donepezil in mild to moderate dementia stages are primarily described as "showing less worsening" compared to placebo. Memantine may have greater benefit in patients with a high prevalence of behavioral and psychological symptoms (delusions, hallucinations, and agitation) for those with more advanced disease, although evidence for end stage disease is lacking. However, studies have demonstrated that there is no additional benefit in adding memantine to donepezil versus memantine alone.[3]

WHAT ARE THE POTENTIAL RISKS AND BURDENS OF DEMENTIA MEDICATIONS IN END-STAGE DEMENTIA?

- Adverse effects such as anorexia, diarrhea, nausea, and vomiting (ChEIs)
- Potential drug-drug interactions
- Increased risk of bradycardia and syncope (ChEIs)
- Burdens and risks associated with taking oral medications when swallowing ability and appetite are decreased
- Memantine dose should be adjusted or stopped in patients with severe renal insufficiency
- High cost

CONSIDERATIONS FOR DISCONTINUING DEMENTIA MEDICATIONS

The following rationale can be used in the decision-making process to support the discontinuation of anti-dementia drugs as an appropriate intervention:[4,5]

- The patient or caregiver (designated health care proxy) chooses to stop treatment
- The patient refuses to take the medication
- The patient does not adhere to the medication regimen, such that continuation would be useless
- There is no response to therapy after a reasonable trial
- The potential benefit of treatment is no longer clinically significant in terms of the overall disease severity/stage:
    - The Functional Assessment Staging Tool (FAST) can be used to identify patients with dementia in the late stage of dementia. A FAST score $\geq$ stage 7A along with one or more specific dementia-related co-morbidities (e.g., aspiration, urinary tract infection, sepsis, multiple stage 3-4 ulcers, persistent fever, weight loss > 10% within 6 months) may be an indicator of a 6-month or less prognosis.
    - Mini-Mental State Examination (MMSE) - score $\leq$ 10 out of possible 30 points.
    - Global Deterioration Scale (GDS) – stage 7
- The patient experiences intolerable side effects:
    - ChEIs – nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, muscle cramps, tremor, dizziness, and headache[2]
    - NMDA antagonists - dizziness, confusion, constipation, and increased blood pressure[2]

APPROACH TO PATIENT'S FAMILY/CAREGIVER FOR DISCONTINUING DEMENTIA MEDICATIONS

- Recognize that it may be difficult for family members to discontinue medications that their loved one has been taking for a long time. Ask what concerns or questions that they might have.
- Help family members to understand that you are prioritizing the medications that are most important right now based upon their loved one's condition and needs.
- Ask the family what symptom(s) improved when their loved one was first placed on the medication. Do they think that it is still helping?
- Recommend a gradual dose taper, carefully observing for any changes in behavior or symptoms. Reassure that you will restart the medication or discuss alternate approaches to managing symptoms if they recur.
- Highlight possible adverse effects associated with dementia medications, including insomnia, nausea and weight loss that may improve once the medications are stopped.[4,5]

Sample Script for Use with Family Members:

"Your mother's dementia medication is most likely no longer contributing to her comfort and may be causing unwanted side effects such as nausea and poor appetite. These medications also increase the burden of taking her pills each day. For these reasons, I suggest that we slowly decrease these medications over the next few weeks while we carefully observe for any changes. Are you OK with that?"

RECOMMENDED DISCONTINUATION PROCESS

- Begin discontinuation with only one medication at a time (often patients are taking ChEI and an NMDA antagonist together)
- Taper the drug by decreasing the dose by half every 4 weeks to lowest available form and then stop. Assess for any reappearance of behavioral or psychological symptoms. If they recur, restart the medication at the effective dose.
- Once the first drug is tapered, begin tapering any other remaining medication in the same manner. If there is no clinical change, stop the medication.
- Patients should be carefully monitored for changes in cognition, function, and behavior following discontinuation of anti-dementia medication. Tapering the dose may minimize the potential of withdrawal syndrome, including agitation, sleep disturbance, and mood changes. If symptoms worsen significantly, consideration may be given to restarting anti-dementia medication.[4,5]

MANAGING PSYCHOLOGICAL AND BEHAVIORAL SYMPTOMS[6-7]

Treat underlying causes of symptoms first:

- Verbal/vocal behaviors - Associated with pain, loneliness, or depression
- Agitation - Associated with pain or boredom and the need for activity and stimulation
- Aggressive behaviors - Associated with avoiding discomfort, the communication of needs or a demand for personal space

Non-pharmacological management initiated first line:

- Monitor personal comfort
- Calm and simplify the environment
- Provide a security object
- Avoid being confrontational
- Acknowledge requests and respond
- Redirect the person's attention
- Psychosocial Interventions (behavioral therapy, cognitive stimulation, physical activity)
- Structured socialization (e.g., pet therapy)
- Other (e.g., music, massage and touch, reminiscence, aromatherapy)

Pharmacological Management

- Serotonin-Selective Reuptake Inhibitors (SSRIs) and Trazodone (Desyrel®)
    - Despite having little statistically significant evidence in controlling depression in patients with dementia, antidepressants have been extensively studied and may be effective in treating agitation and psychotic symptoms in these patients.[8]
    - Both SSRIs (e.g., citalopram (Celexa®), sertraline (Zoloft®)) and trazodone appear to be tolerated well when compared to placebo, typical antipsychotics and atypical antipsychotics for agitation and psychosis in dementia according to a Cochrane database review in 2011.[9]
    - A 2014 study reviewed the addition of citalopram compared with placebo in patients with Alzheimer's disease and found significantly reduced patient agitation and caregiver distress.[1]

- Antipsychotics[11-13]
    - Antipsychotics are associated with an increased mortality when used to treat behavioral disturbances in older patients with dementia. Both atypical (e.g., Risperdal®) and conventional (e.g., Haldol®) antipsychotics are labeled with this black box warning.
    - Despite years of off-label use of this class, atypical antipsychotic drugs are not reliably more effective than placebo for psychotic symptoms of dementia.

    - ***When is antipsychotic use appropriate in the elderly dementia population?***

      Antipsychotics should be used to treat agitation or psychosis in patients with dementia ONLY where environmental manipulation fails and/or when symptoms persist despite non-pharmacological and medication intervention:

        - Behavioral symptoms are due to mania or psychosis
        - Symptoms present a danger to the patient or others
        - Patient is experiencing inconsolable or persistent distress
        - Patient is experiencing a significant decline in function or substantial difficulty receiving needed care
- Nuedexta®
    - Nuedexta® is a combination product containing dextromethorphan and quinidine approved for the treatment of pseudobulbar affect (PBA) in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). PBA is characterized by uncontrollable, sudden, and frequent episodes of laughing and/or crying that do not match the patient's mood. It is thought to result from structural damage to sensory and motor neurons in some patients with neurological disorders such as stroke, MS, traumatic brain injury, Alzheimer's disease, and ALS.[2,14]

    - **Other disease states in which dextromethorphan-quinidine (DM/Q) has been studied**

        - An open-label study enrolling 553 patients with PBA secondary to other neurologic conditions such as Parkinson's disease (PD), Alzheimer's disease (AD), primary lateral sclerosis, stroke, or traumatic brain injury (TBI) demonstrated long-term safety and tolerability of DM/Q.[15] In a recent review of prescribing patterns of DM/Q, investigators found it was primarily prescribed off-label for patients with AD and/or PD.[16]
        - The PRISM II study provided additional experience with PBA secondary to dementia, stroke, or traumatic brain injury (TBI): DM/Q was shown to be an effective and well-tolerated treatment for PBA secondary to dementia, stroke, or TBI.[17,18] Results of the dementia cohort showed significantly reduced PBA symptoms in patients with dementia.[19]
        - Limited evidence suggests that DM/Q may provide some benefit for severe agitation in patients with dementia. When cost is not a concern and other strategies have failed, a trial of dextromethorphan-quinidine may be reasonable.[7,20-29]

REFERENCES:

1. Fairman N, Hirst JM, Irwin SA. Clinical manual of palliative care psychiatry.1st ed. Arlington: American Psychiatric Association; 2016.
2. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2020.
3. Molino I, Colucci L, Fasanaro AM, Traini E, and Amenta F. Efficacy of memantine, donepezil, or their association in moderate-severe Alzheimer's Disease: a review of clinical trials. *The Sci World J*. 2013;1-8.
4. Deprescribing.org. Cholinesterase Inhibitor (ChEI) and Memantine Deprescribing Algorithm. January 2018. Article link
5. Reeve E, Farrell B, Thompson W, et al. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine: Recommendations. Sydney: The University of Sydney; 2018. Article link
6. Clinical Resource, Pharmacotherapy of Dementia Behaviors. Pharmacist's Letter/Prescriber's Letter. June 2022.
7. Press D. Management of neuropsychiatric symptoms of dementia. In: UpToDate. Yaffe K, Schmader KE, Mendez MF, Wilterdink JL, eds. Waltham, MA: UpToDate, Inc; Updated April 7, 2022, with literature review current through May 2022.
8. Wang F, Feng T, Yang S. Drug therapy for behavioral and psychological symptoms of dementia. *Curr Neuropharmacol*.2016 May;14(4):307-313. Article link
9. Seitz DP, Adunuri N, Gill SS, et al. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev.* 2011 Feb 16;(2):CD008191. Abstract
10. Porteinsson AP, Drye LT, Pollock BG. Effect of Citalopram on Agitation in Alzheimer's Disease – The CitAD Randomized Controlled Trial. *JAMA*. 2014 February 19; 311(7): 682–691.
11. Maust DT, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia. Number needed to harm. *JAMA Psychiatry.* 2015 Mar 18. Published online. doi:10.1001/jamapsychiatry.2014.3018
12. Reus VI, et al. The American Association Practice Guidelines on the use of antipsychotics to treat agitation or psychosis in patients with dementia – Executive Summary. *Am J Psychiatry.* 2016 May;173(5):543-546. Article link
13. Salzman C, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: Consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry.* 2008 June*; 69(6):889-898.*
14. Ahmed A, et al. Pseudobulbar affect: Prevalence and management. *Ther Clin Risk Manag.* 2013;9:483-489.
15. Pattee GL, et al. An open-label multicenter study to assess the safety of dextromethorphan/quinidine in patients with pseudobulbar affect associated with a range of underlying neurological conditions. *Curr Med Res Opin*. 2014 Nov 1; 30(11): 2255–2265. Article link
16. Fralick M, et al. Assessment of Use of Combined Dextromethorphan and Quinidine in Patients with Dementia or Parkinson Disease After US Food and Drug Administration Approval for Pseudobulbar Affect. *JAMA Intern Med*. 2019 Feb 1;179(2):224-230. doi: 10.1001/jamainternmed.2018.6112.

17. Hammond FM, et al. PRISM II: an open-label study to assess effectiveness of dextromethorphan/ quinidine for pseudobulbar affect in patients with dementia, stroke or traumatic brain injury. *BMC Neurol*. 2016;16(89):1-12. Article link

18. Hammond M, et al. Safety, Tolerability, and Effectiveness of Dextromethorphan/Quinidine for Pseudobulbar Affect Among Study Participants with Traumatic Brain Injury: Results From the PRISM-II Open Label Study. *PM R.* 2018 Oct;10(10):993-1003. doi: 10.1016/j.pmrj.2018.02.010.

19. Doody RS, et al. An open-label study to assess safety, tolerability, and effectiveness of dextromethorphan/quinidine for pseudobulbar affect in dementia: PRISM II results. *CNS Spectrums* 2016;21:450-459. Article link

20. Cummings JL, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA* 2015;314:1242-54. Article link

21. Ballard C, Sharp S, Corbett A. Dextromethorphan and Quinidine for Treating Agitation in Patients with Alzheimer Disease Dementia. *JAMA* 2015; 314:1233.

22. Shi J, et al. Nuedexta for treating pseudobulbar affect in Alzheimer's disease. ClinicalTrials.gov ID: NCT01832350. Site link

23. Efficacy, Safety and Tolerability of AVP-786 for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type. ClinicalTrials.gov ID: NCT02442765. Site link

24. Efficacy, Safety, and Tolerability of AVP-786 for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type. ClinicalTrials.gov ID: NCT02442778. Site link

25. Long Term, Extension Study of the Safety and Efficacy of AVP-786 for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type. ClinicalTrials.gov ID: NCT02446132. Site link

26. Garay RP, Grossberg GT. AVP-786 for the treatment of agitation in dementia of the Alzheimer's type. *Expert Opinion Invest Drugs*. 2017;26(1):121-132.

27. Chen Q, et al. Effectiveness of Dextromethorphan/Quinidine in Frontotemporal Dementia. *Am J Geriatr Psychiatry*. 2018 Apr;26(4):506. doi: 10.1016/j.jagp.2017.10.008.

28. Kongpakwattana K, et al. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. *Br J Clin Pharmacol.* 2018 Jul;84(7):1445-1456. doi: 10.1111/bcp.13604.

29. Watt JA, et al. Safety of pharmacologic interventions for neuropsychiatric symptoms in dementia: a systematic review and network meta-analysis. *BMC Geriatr.* 2020 Jun 16;20(1):212. doi: 10.1186/s12877-020-01607-7.