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Dementia (E McDade, Section Editor)

Treatment and Management of Dementia Due to Alzheimer's Disease

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Opinion statement

Alzheimer's disease (AD) is a progressive neurological disorder typically associated with episodic memory loss as the initial symptom, but individuals <65 years old may present with executive dysfunction, word finding difficulties, or visual processing deficits. In those with AD, curative treatments are not available, but there are interventions which may modify disease course, symptom appearance and severity, enhance quality of life for patient and caregivers, and maintain safety. Both pharmacological and non-pharmacological interventions are important.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder associated with episodic memory loss in the presence of misfolded amyloid and tau proteins and other pathologies. Patients with AD pathology may be asymptomatic for years prior to the onset of symptoms, progressing through a stage of subjective cognitive impairment with early recognition of changes but no detectable cognitive abnormalities, mild cognitive impairment, where cognition is impaired but functional abilities are essentially intact, prior to developing dementia, in which cognitive symptoms interfere with daily functioning [1]. This paper targets treatment for those with dementia due to Alzheimer's disease as it pertains to clinical practice.

As a part of the Physician Consortium for Performance Improvement (PCPI), the American Academy of Neurology created dementia quality measures, establishing the need for cognitive assessment, dementia staging, behavioral assessment, functional assessment, and screening for depression at least annually in all stages of dementia. Counseling on safety precautions, management of neuropsychiatric symptoms, and caregiver education and support should be integrated into treatment

plans at least annually. Within 2 years of diagnosis or assumption of care, palliative care counseling and advance care plans should be implemented and documented in the chart [2••].

Diet and lifestyle

- A plethora of articles have focused on dietary and lifestyle guidelines in preventing AD. Some of these recommendations include minimizing intake of saturated and trans fats, increasing consumption of vegetables, legumes, fruits, and whole grains, obtaining vitamin E 15 mg daily from foods such as seeds, nuts, and whole grains, getting vitamin B12 2.4 μg daily from foods or supplements, and incorporating 40 min of exercise 3 days/week [3].
- Recommendations also include using supplements with iron or copper as well as products with aluminum sparingly, thought more research is needed to investigate the role of these elements on the development of AD. Sleep and regular mental activity may also be important [3].
- A combination of diet, exercise, cognitive training, and vascular risk monitoring may improve or maintain cognition in those at higher risk for developing dementia (based on cardiovascular risk factors) and those with cognition that is average or slightly lower than expected for age [4•].

Specific recommendations in those with dementia are as follows:

Diet

- The Mediterranean diet which emphasizes the increased consumption of fruits, vegetables, legumes, whole grains, and unsaturated fatty acids, as well as decreased consumption of dairy products, meats, and saturated fatty acids has been well-studied in those with AD. A systematic review of the literature showed that those with higher adherence to the Mediterranean diet had lower risk for conversion from normal cognition to MCI or dementia and conversion from MCI to dementia [5, 6].
- Others, such as the Dietary Approaches to Stop Hypertension (DASH) and a Japanese style diet may be beneficial [6], but further investigation is warranted.

Nutritional supplements

- Antioxidants, vitamins, omega-3-fatty acids, plant flavonoids, medium-chain triglycerides such as coconut oil, herbs such as

huperzine A, and spices such as turmeric all have been studied as potential supplements for AD treatment. However, results have been variable, and further studies need to be performed to determine the relationship between the efficacies of these supplements in those with AD [7].

- There is limited data on the efficacy of nutritional supplements when added to traditional treatments for AD. When added to cholinesterase inhibitors, vitamin E may decrease functional decline but not cognition [8].
- Medium-chain triglycerides produce ketone bodies, an alternative source of energy for the brain. In APOE4-negative patients, the nutritional supplement, Axona, has shown short-term improvement in memory, but primarily for those negative for the apolipiprotein E4 allele. Though based on the same pathway, the use of coconut oil has not been studied to determine its effectiveness in those with AD [7].

Exercise

- A Cochrane database review showed that exercise may improve activities of daily living and possibly cognition in those with dementia. However, due to statistical heterogeneity, caution with interpreting the results is advised. The type, frequency, and duration of exercise also need to be determined [9].
- A recent randomized controlled trial showed that a combination of aerobic and resistance training may be more beneficial than aerobic exercise or social interaction alone [10].
- The Dementia and Physical Activity (DAPA) study in the UK is the largest randomized control trial on investigating the effect of aerobic and resistance exercise in those with dementia [11].

Sleep issues

- Sleep issues are common in those with AD. In the early stages of AD, sleep fragmentation, frequent nocturnal awakenings, and reduction of slow wave sleep may occur. In the later stages of AD, patients may have increased daytime sleepiness, increased REM latency and possible reduction of REM sleep [12].
- In patients with AD, tau pathology in the suprachiasmatic nucleus can lead to an irregular sleep-wake rhythm. "Sundowning" or increased behaviors such as agitation and aggression at nighttime may be heightened by circadian rhythm dysfunction [13].
- FDA-approved medications for the treatment of insomnia include non-benzodiazepine receptor agonists such as zolpidem, zaleplon, and zopiclone; melatonin agonists such as ramelteon, sedating antidepressants such as doxepin; and an orexin-anatogonist, suvorexant.

However, data is limited on the efficacy of these medications in those with dementia, and side effects may worsen cognition especially in sedating anti-depressants.

- Per a Cochrane Database review, more research needs to be performed to determine the efficacy of pharmacological treatments in those with dementia. In moderate-to-severe dementia, trazodone 50 mg in the evening may assist in increasing sleep efficiency, though this medication is not FDA approved for insomnia [14].
- A meta-analysis of melatonin studies by Xu et al. found melatonin therapy may be effective in improving sleep efficiency and prolonging total sleep time without adverse effects, but there is not any evidence that this improvement impacts cognitive function [15]
- Adherence to walking, bright light exposure or a combination of the two interventions during the day may be effective in improving sleep for those with AD [16].
- Look for other sleep disorders. Obstructive sleep apnea can be seen in 33–53 % of patients with probable Alzheimer's disease. If snoring or witnessed apneas are present, further evaluation with polysomnography may be indicated [12].
- Caregiver involvement may be essential in optimizing the sleep-wake cycle in those with Alzheimer's disease [17].

Other lifestyle factors

- Though intellectual stimulation and socialization is encouraged, more studies need to be performed to determine whether these activities can be used to modify cognitive decline in those with dementia [18].

Treatment

Treatment of cognitive and neuropsychiatric symptoms aims to maximize cognitive functioning and enhance the ability to perform activities of daily living. Decreasing burden of caregiving, promoting meaningful interactions that support quality of life, and delaying the need for institutionalization are other goals. At the end of life, treatment shifts to a comfortable death with dignity.

Treatment of cognitive deficits

Acetylcholinesterase inhibitors

- Acetylcholinesterase Inhibitors (AChEI) have class 1A evidence for a statistically significant benefit over basic supportive care for cognition, function, and global outcomes [19, 20]. Efficacy and side effects may be dose dependent.

- Medications in this class include donepezil, rivastigmine, and galantamine. There have been no proven clinically meaningful differences between the agents [21]. If intolerable side effects are present, changing to another agent can be considered.
- Maximal improvement of cognitive measures in mild-to-moderate AD is noted at 3 months on treatment with stabilization lasting for 6–12 months [22].
- AChEI may attenuate decline on cognitive scores and faster decline is evident when treatment is stopped; however, evidence of a more rapid decline has not been definitively proven [23].
- Duration of treatment is not well established, but trials have demonstrated benefit at 4 and 7 years [24, 25].
- Meta-analysis results suggest that the efficacy of AChEI on cognition is beneficial for all stages of disease severity [26].

Class effects

Contraindications	Bradycardia and heart block. Caution in epilepsy. Active gastric ulcers/gastritis, steroid-dependent asthma/chronic obstructive pulmonary disease, and pneumonia.
Main drug interactions	CYP2D6 substrate and CYP3A4 substrate Beta-blockers exacerbate bradycardia. Medications that inhibit the effects of donepezil include antibiotics such as ciprofloxacin clarithromycin, or erythromycin. Medications with anticholinergic effects such as tricyclic antidepressants (TCAs), cyclobenzaprine and bethanochol may interfere with AChEI effects. Non-steroidal anti-inflammatory drugs increase bleeding risk. TCAs and bupropion may have additive effects on lowering the seizure threshold. Exaggerates succinylcholine-type muscle relaxation during anesthesia.
Main side effects	Nausea, vomiting, diarrhea, anorexia, dizziness, muscle cramps, fatigue, and vivid dreams. Bradycardia may cause syncope. Side effects are usually dose dependent.
Cost effectiveness	All AChEIs were more cost effective than basic supportive care [19].
Special points	Recommend taking with breakfast to reduce insomnia, nightmares, and nausea. Long-acting formulations may be better tolerated.

Donepezil (Aricept)

Standard dose	Oral 10 mg daily or extended release formulation 23 mg daily
Contraindications	See "Class Effects."
Main side effects	See "Class Effects."
Drug interactions	See "Class Effects."
Special points	FDA approved for mild, moderate, and severe Alzheimer's dementia. Start 5 mg daily with breakfast × 30 days followed by 10 mg × 90 days. Consider an increase to 15 mg daily for 30–90 days followed by 20 mg daily or 23 mg daily for moderate-to-severe dementia. However, there may be relatively little benefit and a clear increase in side effects with the 23 mg dose.
Cost	Generic 10 mg, $110.00 (30 tabs) Aricept disintegrating tablet, $400.00 (30 tabs) Aricept 23 mg, $400.00 (30 tabs)

Rivastigmine (Exelon)

Standard dose	Transdermal 4.6–13.3 mg/24 h Oral 1.5 mg twice daily to 6 mg twice daily
Contraindications	See "Class Effects."
Drug interactions	See "Class Effects."
Main side effects	See "Class Effects."
Special points	FDA approved for mild, moderate, and severe Alzheimer's dementia
Oral	Start at 1.5 mg twice daily; increase each dose by 1.5 mg every 2–4 weeks; max dose 6 mg twice daily. Best taken with food. Re-titrate if treatment is interrupted >3 days. Oral tablets are often poorly tolerated; consider switch to patches
Transdermal patch	Start at 4.6 mg/24 h for 1 month; can increase to 9.5 mg/24 for 1 month then 13.3 mg/24 h (moderate-to-severe dementia) thereafter
Cost	Exelon patch 4.6, 9.5, and 13.3 mg, approximately $300.00 (30 patches) Exelon oral solution 2 g/mL (120 mL), $540.00

Galantamine (Razadyne)

Standard dose	At 16–24 mg daily. Immediate release formulation is divided into twice a day dosing.
Contraindications	See "Class Effects." Discontinue if QTc interval >500 ms
Drug interaction	See "Class Effects." Medications that prolong the QTc interval.
Main side effects	See "Class Effects."
Special points	Oral 8 mg daily for 30 days followed by 16 mg daily for 30 days, then 24 mg daily. Consider increasing to 32 mg daily for cognitive symptoms or treatment of neuropsychiatric symptoms. • May be beneficial in mixed AD with cerebrovascular disease [22] • Prolongation in the QTc interval can occur. • Monitor potassium and magnesium levels, which can exacerbate arrhythmia.
Cost	Galantamine 8 mg tabs, $520.00 (60 tabs) Razadyne ER 16 mg, $270.00 and 24 mg, $835.00 (30 tabs)

N-Methyl-D-Aspartic acid receptor antagonists

- A meta-analysis of randomized controlled trials supports evidence for stabilization of cognition, functionality, behavior, and caregiver distress in patients with moderate to severe AD with memantine [26].
- Memantine was well tolerated [20].

- Can be used as monotherapy or prescribed with an AChEI. A synergistic effect has been observed with use of both an AChEI and memantine to slow the rate of cognitive decline in those with moderate dementia [23].

Memantine (Namenda)

Standard dose	Ten milligrams twice daily or extended release 28 mg daily
Contraindications	Allergy. Caution in severe renal disease
Drug interactions	Some anti-arrhythmic medications such as procainamide, quinidine, and flecanamide compete for renal clearance and increase serum levels of both drugs. Midodrine.
Main side effects	Headache, constipation or diarrhea, and worsening confusion or agitation.
Special points	FDA approved for moderate-to-severe Alzheimer's dementia.
Intermediate release titration	Start 5 mg PO daily, then increase by 5 mg/day each week until 10 mg twice daily
Extended release titration	Start 7 mg × 1 week, then 14 mg × 1 week, then 14 mg × 1 week then 28 mg daily. Both immediate release and extended release have "starter packs."
Cost	Namenda 10 mg twice daily, approximately $300.00 Namenda oral solution 10 mg/5 mL, approximately $600.00 Namenda XR 7, 14, 21, and 28 mg. Manufacturing issues since May 2014 have interfered with availability. Approximately $700.00 for 30 tabs.

Other considerations

- A practical treatment algorithm has recently been published [27].
  - For mild-to-moderate AD, monotherapy is recommended with an AChEI.
  - In moderate-to-severe AD, monotherapy or a combination of an AChEI with memantine can be considered.
  - Patients should be monitored for side effects or abrupt change.
  - Discontinuing medications should be considered if the patient has severe loss of cognitive and functional abilities.
- Switching AChEIs can be considered if the medication is not tolerated or becomes ineffective. Resolution of side effects is recommended prior to switching to another AChEI due to intolerance. If there is no benefit on cognition or function after one year of treatment, switching to another AChEI can be switched immediately. However, if the patient is showing progression of symptoms after initiating the medication, adding memantine may be more beneficial than switching to another AChEI [28•].
- Clinical judgment is advised, including an assessment of medication compliance and other co-morbidities prior to adjusting medications [28•].

- Treatment of neuropsychiatric symptoms and non-pharmacological strategies also should continue to be addressed.

Treatment of neuropsychiatric symptoms

Non-pharmacological strategies

- Although cognitive impairment is the clinical hallmark of AD, neuropsychiatric symptoms (NPS) are exceedingly more common and dominate the presentation [29]. Providers are often called upon to "fix" NPS; however, no pharmacologic solution addresses potential underlying causes of behaviors that may be most distressful to families [30].
- Non-pharmacological strategies are recognized as first-line treatment for neuropsychiatric symptoms of Alzheimer's dementia [29, 30].
- Non-pharmacologic interventions aim to provide the caregivers with the competence and skills to tolerate and manage problematic behaviors. In addition, interventions are targeted at the affected person address basic intellectual, psychosocial, or physical human needs. The overall goal of therapy is to promote a supportive psychosocial, physical, and cognitively stimulating environment that enhances quality of life for both the individuals with Alzheimer's disease and the immediate caregiver(s) [31–33].
- The most effective programs for treating NPS use a variety of interventions that are individualized to both the caregiver and care recipient who each bring unique characteristics to the relationship. The programs are intensive, usually requiring multidisciplinary teams [31–33, 34••]. Effective programs may delay nursing home placement. In those already in a nursing home, non-pharmacological strategies have equal or higher efficacy than pharmacological treatments without the risk of harm.
- Family caregivers are critical to maintaining recipient's health, safety, and enabling the patient to stay at home. Providers need to monitor for caregiver burden which can be assessed with a variety of tools from simple screens to in-depth assessments through resources such as the Family Caregiver Alliance and the Alzheimer's Disease Association [35].
- Annual systematic screening for NPS with a reliable tool such as the Neuropsychiatric Inventory Questionnaire [36] and implementation of preventive action plans is recommended [2••]. While most office visits may be time-limited in providing comprehensive assessments and guidance through a problem-solving process, providers can collaborate with social workers or train nursing staff to make appropriate referrals.
  - Screen for NPS at each visit. If not present,

    Provide resources about dementia, dementia stages, and common behavior symptoms relative to the stage.

Reinforce importance of early detection of behavior issues and notification of health care provider.
Reinforce need of the individuals with AD to have adequate stimulation and a structured daily routine.
Counsel caregivers of the importance of self-care and emphasize their prominent role as caregiver in the treatment plan.

– Screen for and address behavioral risk factors including

Caregiver distress
Patient pain
Sleep disturbance
Inadequate nutrition
Infection or acute illnesses, including dental disease and constipation
Medication interactions or changes (try to remove anti-cholinergic meds)
Absence of routine (irregular bedtime and waking hours, meals, activities, caregivers)
Absence of physical, cognitive, and social stimulation
Sensory loss (sight, hearing)
Safety

– When behaviors are present, a more formal assessment and intervention is required. One approach is the evidence informed descriptive model developed by a team of experts—"**DICE**" [29].

Describe the behavior: ask the caregiver to describe an NPS event "as if in a movie." If possible, get recipients input as well.
Investigate to identify possible causes of the problem behavior: look at antecedents leading up to behavior and identify possible triggers, such as pain, fear of falling, boredom, pain, and caregiver fatigue.
Create a management plan:

- Address medical and physical factors, e.g., antibiotics for urinary tract infection, discontinuation of sedating medications and review sleep hygiene.
- Address caregiver needs such as a referral to psychologist for depression or a referral to support groups and caregiver dementia training to build appropriate skills to approach patient with NPS. In-home occupational therapy may be appropriate for home safety assessment, maximizing and supporting activities of daily living, adjusting the physical environment and finding appropriate pleasurable stimulating activities.
- Brainstorm strategies with caregiver to decrease frequency and severity of most problematic behaviors by avoiding triggers or preventing escalation, e.g., using a calm voice.
- Reinforce that pharmacologic strategies have limited effect on behaviors and put the patient at undue risk. Use only if mitigating strategies fail.

Evaluate: Identify strategies that are working and make refinements as needed.

Pharmacological treatment

- Approximately 97 % of patients will experience at least one NPS. Most commonly reported are depression, anxiety, or apathy [29, 37].
- Anxiety, depression, aggression, delusions, and disinhibitions tend to be perceived as "severely" or "extremely" distressing by caregivers [38].
- Untreated NPS can lead to increase mortality, caregiver burden, earlier nursing home placement, and exaggerate cognitive and functional disabilities.
- Recognizing the negative impact of NPS, the PCPI established metrics to decrease NPS severity and frequency, which can be found at http://www.ama-assn.org/ama/pub/physician-resources/physician-consortium-performance-improvement.page.
- There are no FDA-approved pharmacotherapies to treat NPS in dementia. However, pharmacological interventions are necessary when non-pharmacological interventions are unsuccessful, symptoms are severe enough for patient or caregiver harm, or when patient exhibits psychosis of AD [39]. The thresholds for severity remain unclear [40].
- Consider targeting treatment toward the most distressing presenting symptoms and matching to the most relevant drug class.
- Restlessness, non-purposeful activity, unfriendliness, poor self-care, emotional disengagement, repetitive verbalizations of questioning, rejection or refusal of care, shadowing, and wandering may not likely be affected by psychotropic medication.

Apathy

- Apathy is associated with diminished motivation of goal-directed behavior. It is characterized by emotional indifference and lack of initiation and interest in daily activities and interpersonal relationships. Symptoms of apathy overlap with depression, are difficult to distinguish, and often occur together [41–43].
- NPS in persons with AD tend to occur early in the disease process and with increasing frequency as the disease progresses [42].
- The likely pathology of AD-related apathy results from cholinergic deficits and neuropathic changes in brain areas such as the anterior cingulate, frontal-subcortical circuit that are important for both the cognitive momentum to complete thoughts or actions, and the assignment of an appropriate affective value [41].
- Apathy adversely effects functional independence [42]. Caregivers are required to meet basic needs for patients unmotivated to act.
- Non-pharmacological recommendations are to optimize levels of appropriate stimulation and activities and to provide caregiver support to tolerate apathy.

- Best evidence for pharmacological treatment of apathy includes any AChEI. Memantine, psychostimulants, and atypical anti-psychotics may be considered, though there is insufficient evidence to support their use [42].

AChEIs including Donepezil, Galantamine, and Rivastigmine

- Level II evidence for modest effect in AD-related apathy. A review of one randomized controlled trial and eight open label studies that included a total of 7655 patients treated with AChEI (6752 on rivastigmine) concludes that 379 (4.95 %) had improved apathy scores that reached statistical significance [42, 43].

Memantine

- Level II B (two double-blinded randomized controlled trials) supports significant improvements in apathy levels [42]. Doses may be beneficial at 10–30 mg daily.

Amphetamines

- Two small randomized controlled trials for methylphenidate 10 mg twice a day suggest a modest improvement in arousal, processing speed, and some aspects of motivation, but doses were often decreased due to side effects [43].

Anxiety/Depression/Irritability

- Serotonergic and dopaminergic neurotransmission is impaired in AD and likely contributes to depressive, anxious, and agitation symptoms. The exact mechanism of depression related to AD is not understood. More recent neuropathological studies suggest alterations in glutamatergic transmission [44].
- Non-pharmacologic treatment includes setting expectations at a patient's level of ability and creating pleasurable experiences. In addition, psychological treatments can reduce depressive symptoms in people with dementia [45].
- A recent review of ten randomized controlled trials and three meta-analyses that examined the evidence for efficacy and safety of anti-depressants in treating depression in dementia was inconclusive [46].
- In addition, selective serotonin reuptake inhibitors (SSRIs) have been associated with increased falls in nursing home patients. Treatment recommendations are to treat significant persistent depressed mood with an SSRI based on minimal anti-cholinergic activity [46].

Selective serotonin reuptake inhibitors

Citalopram

Standard dose	Ten to forty milligrams daily
Contraindications	Gastrointestinal bleeding; monoamine oxidase inhibitors. Not recommended in those with bradycardia, uncompensated congestive heart failure, congenital QT prolongation syndrome, hypokalemia, recent myocardial infarction, and hypomagnesaemia. Discontinue with QTc interval >500 ms.
Drug interactions	CYP2C19 substrate, CYP2C19 weak inhibitor, and other serotonergic drugs Medications with antiplatelet effects medication that lower sodium (hydrochlorothiazide, carbamazepine). Medications that prolong QTc (antipsychotics, odansetron). Serotonergic medications (fentanyl, TCAs, antipsychotics).
Main side effects	Gastrointestinal distress, anorexia, weight loss, sedation, insomnia, sexual side effects, and paradoxical agitation. Prolonged QT interval.
Special points	A maximum dose of 20 mg/day in individuals >60 years is recommended by the FDA for risk of arrhythmia due to QTc interval prolongation. Twenty-milligram dose typically increases QTc by 5.3–7.9 ms, and 40 mg dose typically increases QTc interval by 12.6 mg (90 % CI, 10.9–14.3 ms) [47].
Cost	Ten milligrams, $80.00 (30 tabs); 20 mg, $100.00 (30 tabs); 40 mg, $90.00 (30 tabs); and 10 mg/5 mL (240 mL), $200.00

Sertraline

Standard dose	At 50–200 mg/day
Contraindications	Monamine oxidase inhibitors and pimoside
Drug interactions	CYP2C19 substrate, CYP2D6 substrate, CYP3A4 substrate, and CYP2D6 weak inhibitor (some anticonvulsants, antipsychotics, benzodiazepines, antiarrhythmic, antibiotics), other serotonergic medications (triptans TCA, cyclobenzaprine, tramadol, fentanyl), and NSAIDs anti-platelet and anticoagulant agents
Main side effects	Diarrhea (may appear at any time after initiating treatment), anorexia, weight loss, sedation, insomnia, sexual side effects, and paradoxical agitation.
Special points	Start at 25–50 mg daily. May increase in 2-week intervals. Effect may not be appreciated for 4–6 weeks. Taper off to discontinue.
Cost	Sertraline 50 mg, $16.00 (30 tabs) and 100 mg, $19.00 (30 tabs). Oral solution 20 mg/mL and 60 mL, $100.00

Aggression/Agitation

- There are variable definitions of "clinically significant aggression and agitation" that may be characterized by a range of mood, verbal and motor disturbances such as calling out, cursing, threatening or actual physical aggression or combativeness, pacing, and wandering.

- Acute psychomotor delirium or agitation may be considered a medical emergency and may require immediate treatment [48].

AChEI and Memantine

- Treatment with AChEIs has best evidence for benefit in mild-to-moderate symptoms; there is little benefit for severe agitation or aggression [49]. Benefit may be seen with donepezil 10 mg and galantamine 24 mg dosing [20].
- Memantine had no clear benefit for severe NPS [23].

SSRIs

- Evidence (randomized controlled trial, limited studies, class B evidence) of benefit for anti-depressant vs. placebo to reduce agitation and psychosis is fair quality [50]. Evidence is strongest for citalopram (escitalopram) and sertraline. These SSRIs may be equal to anti-psychotics with better side effect profile [51, 52].
- SSRIs may improve NPS by modulating serotonergic neurotransmission that may be impaired in AD [50].

Citalopram

Standard dose	Studies used doses of 30–40 mg/day, which is above the recommended doses of 20 mg for individuals older than 60 years.
Contraindications	See above.
Main side effects	See above.
Special points	Citalopram 30 mg daily may be equivalent to risperidone 1.25 mg/day for aggression and hostility [51]. In the recent Citalopram for Agitation in Alzheimer Disease (CitAD) Study, citalopram 30 mg daily also was more effective than placebo in improving agitation and caregiver distress [52]. Note again that both of these studies used doses that were above the recommended doses of 20 mg in individuals older than 60 years old. Caution is advised for cardiac adverse effects if the 30 mg dose is used.
Cost	See above.

Sertraline

Standard dose	At 50–200 mg.
Contraindications	See above.
Main side effects	See above.
Drug interactions	See above.
Special points	See above.
Cost	See above.

Non-sedating, non-benzodiazepine anxiolytic partial 5HT receptor agonists

- Modest efficacy (no randomized controlled trials, many open label, class C evidence) for anxiety, mixed anxiety/depression, agitation and aggression without the sedation, and falls associated with psychotropics and benzodiazepines [53].

Buspirone

Standard dose	At 5–20 mg three times a day.
Contraindications	Monoamine oxidase inhibitor use for 14 days (due to hypertension), linezolid, and methylene blue.
Drug interactions	Grapefruit increases levels and should be avoided. Buspirone increases effects of Haldol. CYP3A4 substrate, strong serotonergic effects; CPY3A4 substrate (avoid inhibitors like ketoconazole). Increase effects of warfarin.
Main side effects	Dizziness, headache, sleep disturbances, and gastrointestinal disturbance.
Special points	Start 5 mg twice a day or three times a day, then increase by 5 mg daily every 2–3 days. Maximum dose is 60 mg/day.
Cost	Five milligrams, $45.00 (90 tabs); 10 mg, $100.70 (60 tabs); 15 mg, $100.00 (60 tabs); and 30 mg, $150.00 (60 tabs).

Mood stabilizers

- Although frequently used, a systematic review concluded that valproic acid and divalproex are not effective in treating aggression or agitation in Alzheimer's disease, can cause brain volume loss, and may accelerate cognitive decline [54]. There is insufficient data for management of NPS with lamotrigine, oxycarbamazepine, topiramate, or gabapentin [55].

Carbamazepine

- Some benefit over placebo in a randomized controlled trial for management of agitation (evidence "C," inconsistent patient-oriented evidence) [56].

Standard dose	Average dose 300 mg (low dose compared with seizure or bipolar disorder).
Contraindications	Avoid with TCA (especially nefazadone) and monoamine oxidase inhibitors.
Main side effects	Sedation, hyponatremia, leukopenia, ataxia, postural instability, rash, weakness, and disorientation.
Drug interactions	Strong enzyme inducer of CYP450 3A4 and keep acetaminophen doses to max dose 2 g/day.
Special points	Black box warning for toxic epidermal necrolysis and Steven-Johnson Syndrome. Monitor for aplastic anemia and suicide. Limit use in the very old due to increased risk of side effects (falls and sedation). Start 100 mg twice a day then increase to every 8 h.

Cost	Carbamazepine 100 mg chewable, $30.00 (90 tabs); 200 mg tablet, $12.00 (60 tabs); and 200 mg ER, $80.00 (60 tabs)

Benzodiazepines

There are multiple recommendations in the literature to avoid chronic use in elders. There is a paucity of evidence for use of benzodiazepines for psychosis or NPS in dementia in clinical trials. For acute aggression or delirium in an individual with AD, "rescue" treatment with benzodiazepines may be appropriate [48].

Lorazepam

Standard dose	Lorazepam 0.25–1.0 mg by mouth as needed.
Contraindications	Avoid rescue treatment with benzodiazepines in individuals with respiratory disease.
Main side effects	Sedation, falls, and confusion in chronic use. Case studies of paradoxical agitation. High risk of respiratory depression.
Special points	Frequently implicated for inducing delirium and worsening pre-existing cognitive impairment. Risk of tolerance and dependency with long-term use. First-line treatment for acute aggressive agitation for patients with Parkinson's disease or Lewy body disease.
Cost	Lorazepam 0.5 mg, $13.00 (30 tabs); 1 mg, $15.00 (90 tabs); and 2 mg, $25.00 (30 tabs). Solution 2 mg/mL (30 mL), $60.00.

Hallucinations/Delusions/Paranoia with or without aggression

AChEI and/or Memantine

- AChE-I have small but significant effect over placebo in mild-to-moderate symptoms but not acute aggression (classes A–B) [49].
- Memantine may benefit mild-to-moderate irritability, agitation or aggression, and psychosis over 3–6 months (class A–B) [57].

Conventional antipsychotics

- Antipsychotics may improve on aggression and psychosis but are poorly tolerated [58].
- Limited by side effects: extrapyramidal symptoms, sedation, falls, orthostatic hypotension, prolonged QTc interval, snd tardive dyskinesia.
- Conventional antipsychotics have higher rates of cerebrovascular adverse events and death than atypical antipsychotics [59].
- A retrospective case–control study on 90,786 participants reports an increased risk of mortality (3.8 % for haloperidol, 3.7 % for risperidone, 2.5 % for olanzapine, and 2.0 % for quetiapine). Higher doses increased risk [60].

Haloperidol

Standard dose	Chronic symptoms 0.5–5 mg twice a day or three times a day. Start 0.5 mg twice a day to three times a day. For acute psychomotor agitation, 5 mg IV or IM.
Contraindications	Concomitant use of solid potassium formulations, medications with known effects to prolong QTc interval, quinidine. Interacts with warfarin, certain antibiotics, etc. Congestive heart failure and recent myocardial infarction.
Main side effects	Tardive dyskinesia, EPS, dystonia, anticholinergic effects, sedation, orthostatic hypotension, and cognitive impairment.
Special points	Prescribing practice has changed since 2008 in response to specific concerns about the adverse effects of typical anti-psychotics. Haloperidol remains a controversial treatment of aggression and psychosis in dementia [40]. Check ECG for baseline QTc. It is our opinion that haloperidol should never be used in those with dementia.
Cost	Haloperidol 0.5 or 1 mg (30 tabs), $12.00; 2 mg, $23.00 (30 tabs); and 5 mg tab, $4.00 (30 tabs).

Atypical antipsychotics

Class Effects

- Efficacy is modest for benefit on NPS (randomized controlled trials, good evidence) and appears to be most effective in reducing anger, hostility, and psychosis [54, 57, 60, 61] There are high rates of intolerable side effects of olanzapine and risperidone [62•]. Evidence level II–III, A–B.
- Strongest evidence for effect on NPS is for risperidone (Class I randomized controlled trial studies, well done). Approved for use in the UK, Australia, and Canada for psychosis in dementia. There is additional evidence supporting efficacy to treat NPS with olanzapine and aripiprazole [55, 61, 63]; however, benefit may be small.
- Atypical antipsychotics were associated with worsening cognitive function that is both statistically significant and clinically relevant [62•, 64]
- In 2005, the FDA issued a black box warning for use of atypical antipsychotics in people with dementia based on 17 placebo-controlled trials which reported an increased risk of death that is 1.6–1.7 times the rate of placebo (number needed to harm (NNH) varied from 26 to 87) and stroke (NNH=53) [63, 65••].
  - Death was most often attributed to cardiovascular events or infection.
  - Risk is evident by 30 days and absolute risk of mortality increases over time [40, 59].
  - Efficacy, safety, and tolerability thus should be carefully considered against clinical need [66].
    - Consensus recommendations suggest use of atypical antipsychotics as first-line agents only in presence of major depression, psychosis with risk of harm, and aggression with risk of harm. Discuss risks, benefits, and goals of treatment with caregivers. Evaluate response to treatment and monitor for side effects. Stop if ineffective or unacceptable side effects. Use low

	doses. Wean off as soon as possible [29]. Results of the dementia antipsychotic withdrawal trial (DART-AD) demonstrated a doubling of survival rates at 3 years in patients randomized to the cease antipsychotic treatment arm (class A) [67]. • Discontinuation of antipsychotics in most individuals on chronic treatment did not exhibit worsening behavior (higher risk of exacerbation in those on high doses and with more severe NPS) [68]. Consider discontinuation of antipsychotics unless two previous attempts led to clear exacerbation.
Contraindications	Hypersensitivity to drug class, low potassium, low magnesium, congenital prolonged QTc, and arrhythmia. Discontinue for a QTc interval >500 ms. Multiple cautions include hepatic impairment, diabetes, leukopenia, Parkinson's, or Lewy body disease
Main side effects	Sedation, orthostatic hypotension, fall-related injury, weight gain, elevated glucose, dyslipidemia, extrapyramidal symptoms, worsened cognitive impairment, and anti-cholinergic effects. Increased urinary and upper respiratory infections.
Drug interactions	Additive effect with hypotensive agents, sedating agents, serotonergic agents, and anti-cholinergic agents. Watch additive effect on QT interval, e.g., ciprofloxacin
Special points	Lowers seizure threshold. Follow complete blood count.

Quetiapine

Standard dose	At 50–200 mg
Contraindications	See "Class Effects."
Main side effects	See "Class Effects."
Drug interactions	See "Class Effects."
Special points	Quetiapine has lowest association with mortality, but it also has least evidence of beneficial effect. Moderate level of strength of evidence for use in agitation with prominent generalized anxiety. It is equally effective as paroxetine and escitalopram to treat anxiety [63].
Cost	At 25 mg, $310.00 (60 tabs); 50 mg, $500.00 (60 tabs); 100 mg, $510.00 (60 tabs); 200 mg, $875.00 (60 tabs); 300 mg, $1200.00 (60 tabs); and 400 mg, $1325.00 (60 tabs).

Risperidone

Standard dose	At 0.5–3 mg. Start 0.25 mg daily then increase by 0.25–0.5 mg/day every week. Doses greater than 4 mg are rarely more effective. Study doses typically 0.5–2 mg/day (class IB).
Contraindications	Pre-existing leukopenia or neutropenia.
Drug interactions	See "Class Effects."
Main side effects	Orthostatic hypotension.
Special points	Consensus recommendations suggest maximum doses of 1.0 to 1.5 mg/day. • May be helpful for agitation with obsessive-compulsive behaviors [63].
Cost	At 0.25 mg, $80.00 (60 tabs); 0.5 mg, $150.00 (60 tabs); 1 mg, $100.00 (60 tabs); 2 mg, $270.00 (60 tabs); 3 mg, $600.00 (60 tabs); and 4 mg, $300.00 (60 tabs).

Olanzapine

Standard dose	At 5–10 mg/day. Start 2.5–5 mg by mouth daily in older adults, female or those with risk for hypotension. Increase by 2.5 mg daily every 1–2 weeks. Doses >10 mg daily rarely more effective
Contraindications	Do not give with solid potassium dose formulations. Discontinue if absolute neutrophil count <1000/mm^3.
Drug interactions	See "Class Effects."
Main side effects	More anti-cholinergic effects than others in this class.
Special points	May have more benefit on aggression than psychosis.
Cost	At 2.5 mg tab, $11.00; 5 mg, tab $13.00; 7.5 mg, $14.0; and disintegrating tabs, $50–100/tab.

Third-generation anti-psychotics (Partial D2 Receptor Agonist)

- Also called dopamine stabilizers. Act as agonist in areas that dopamine concentration is low and antagonist where dopamine levels are high. Lack effects in areas of normal dopamine levels, notably the nigral striatum.

Aripiprazole

Standard dose	Start 2 mg by mouth daily for 1 week. Increase to 5 mg by mouth daily and then 5 mg/week. Goal dose is 5–10 mg daily. Average dose for efficacy is 10 mg. Doses greater than 15 mgday are rarely effective.
Contraindications	Discontinue for absolute neutrophil count <1000/mm^3.
Main side effects	Somnolence (8 %) and accidental death (8 %). Worsened cognitive impairment (0.8 point drop on Mini-Mental State Examination), orthostatic hypotension, tachycardia, decreased seizure threshold, tremor, and gastrointestinal disturbances [69]
Special points	Extrapyramidal symptoms, weight gain, prolactin elevation, cardiovascular adverse effects, and electrocardiogram changes equal to placebo. Mintzer et al. reports mortality rates appear to be dose related: placebo, 3 %; 2 mg dose, 3 %; 5 mg dose, 2 %; and 10 mg dose, 7 % but deemed not statistically significant [70]. No deaths in the treatment arm [69]. Good evidence for management of psychosis [70].
Cost	At 2 mg, $775.00 (30 tabs); 5 mg, $785.00 (30 tabs); 10 mg, $760.00 (30 tabs); 15 mg, $690.00 (30 tabs); and 20 mg, $1,055.00 (30 tabs)

Emerging therapies

- Currently available drugs such as the acetylcholinesterase inhibitors may improve cognitive and behavioral symptoms but do not change the progression of the underlying pathology of AD [71].

- Agents that block amyloid production or improve amyloid clearance have failed to show benefit bringing into question the amyloid hypothesis, but the timing of intervention with these therapies may be a reason for their lack of efficacy [71].
- An important consideration is that clinically apparent AD is the manifestation of a disease process that is 10–25 years in the making. Research is also being directed toward identification of appropriate biochemical markers of preclinical AD and preventing clinical symptoms as a long-term goal [72].
- Agents that target protein misfolding, mitochondrial dysfunction, tau phosphorylation, and diabetes, which have shown promise and are under current investigation [71].
- In addition to drug modulating therapies and cognitive enhancing drugs, there are ongoing evaluations of medications to target the distressing NPS of AD.

  – Non-pharmacological strategies including activity therapy, home occupational therapy interventions, and transcranial magnetic stimulation are currently under investigation with support from NIH.
  – Medications with better side effect profiles are also being studied to address depression, agitation, aggression and psychosis. A small randomized controlled trial of the alpha-adrenoceptor blocker prazosin indicates potential benefit in the treatment of NPS in AD patients and a large RCT is underway (class B evidence) [73].

Caregiver education and support

- Caregivers need to be formally established and not assumed. They are an essential component of the treatment plan and should be aware of their role, the need for training and support from other individuals and institutions, and the importance of preventive strategies for "burnout." Especially with spouses or elderly caregivers, clinicians should carefully assess the caregiver's own cognitive abilities; a failure to implement caregiving plans or persistent failure of non-medical interventions may signal an impaired caregiver.
- Caregiver education and support require both general information and treatment strategies that are individualized to each unique dementia care recipient-caregiver dyad. The progression of AD may follow a predictable progression, and the person with AD will exhibit various neuropsychiatric symptoms at various points along the trajectory. However, the type of neuropsychiatric symptoms, severity, frequency, and response to treatment will vary across individuals [34••].
- Baseline personalities should be considered. The caregiver, on the other hand, may not perceive themselves as a natural caregiver or resent being placed in the caregiver role. Personality characteristics such as flexibility, creativity, pessimism, sense of humor, and willingness to sacrifice may affect how the

caregiver is able to adapt as the zIizndividual with AD changes [34••].

- Moreover, general health, strength, and size of social networks and finances will influence the caregiver's response and sense of burden. As the disease progresses, the caregiver has to face a series of losses while developing more sophisticated strategies to support a more dependent loved one [34••].
- Finally, the historical relationship between the caregiver and recipient will influence the dyad throughout the disease. The dyad relationship is dynamic. Positive or negative changes in the behavior of the individual with AD similarly influence changes in caregiver behavior and vice versa. Therefore, each individual with Alzheimer's disease will be treated uniquely based on symptoms that can be tolerated and managed by the caregivers in their life to maximize quality of life of all involved [34••].
- Programs for support may include seminars/lectures, structured peer group sessions, psychotherapy, or dementia care training

Safety precautions

- Those with dementia are at higher risk for falls. Assessing for fall risk and providing suggestions to mitigate fall risk is warranted in patients with AD dementia [74].
- Those with dementia are at a higher risk for driving. Assessing for driving risk is also warranted in those with AD dementia. Patients may need to discontinue driving and take a driving evaluation. Suggesting alternative transportation may assist in easing the transition [75].
- Medication adherence may also be challenging in those with dementia. Oversight with medications and aids to remind patients to take their medications may be useful in patients with AD dementia [76].
- Other safety precautions include removing harmful objects from the household, including firearms [27].

Palliative care and advance care planning

- End of life planning should begin early. The American Academy of Neurology/American Medical Association/Centers for Medicare and Medicaid Services quality performance measures require palliative care counseling and advance care plans to be implemented within two years of diagnosis or assumption of care [2••]. The documents should be placed in the chart.
- Early consideration of end of life issues reduces stress of introducing end of life planning at a critical juncture, ensures patient input and identification of patient centered meaningful goals, and eases family and caregiver burden of trying to guess or estimate patient wishes at times of critical change. Additionally, other terminal conditions may

occur and often do before severe dementia stages are reached. Overall, the goal is a "good death."

- Counseling should include:
  - Elder law referrals for legal and financial planning which provide the most benefit if initiated early
  - Preparation of advanced directives
  - Initial identification of end of life wishes. Revisit these goals and directives at least every 2 years throughout disease course. Caregivers should be integrated into the discussion early but in later stages, they may be more integral to the discussion.
- Cognition should be measured annually and function staged to determine proactive identification of patient and caregiver needs and rate of change for prognosis purposes. Acceleration in the annual rate of decline is associated with an inflection point from severe dementia to terminal decline and indicates likelihood of death within 2 years. On the other hand, a rapid change occurring in earlier stages suggests medical comorbidity which potentially can be identified, treated, and/or considered in overall prognostication (infection, metabolic, medication side effect, inflammatory/paraneoplastic, sleep apnea, impaired sleep hygiene, etc.). Cognitive status can be measures with screening mental status examinations, formal neuropsychological testing. Functional staging can be measured with items such as the Clinical Dementia Rating scale [77].
- Other medical conditions may intervene, such as congestive heart failure or cancer and need to be incorporated in staging and prognostication
- Identify and encourage interaction with community hospice and specialty resources (e.g., Alzheimer's Association, Parkinson's Association).
- Future initiatives are being devised to adopt technology to aid in end-of-life planning [78]. There is limited benefit of current advanced directives tool due to low completion rates, lack of availability when needed, lack of current tools for helping patients and families identify personal values, and inability to easily modify these tools as disease progresses, other diseases intervene, and support systems change. Web-based tools should be developed such as clouds, chat rooms, Webinars, Internet support groups, and multimedia capabilities with interactive software that can better target and engage different groups (e.g., children, different ethnic and cultural groups, non-English speakers, etc.).

Conclusions

A comprehensive approach is warranted in the treatment and management of those with AD. Treatment is currently symptomatic. Non-

pharmacological strategies, caregiver support, and safety precautions should be considered.

Compliance with Ethics Guidelines

Conflict of Interest

Jennifer Rose V. Molano, Robin Bratt, and Rhonna Shatz declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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