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Management Guidelines for Alzheimer's Disease and Related Dementias

Sponsored by the Georgia Department of Human Services.
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Clinical Management Guidelines
Alzheimer's Disease, Lewy Body Dementia, Vascular/Mixed Dementia, and Frontotemporal Dementia

Healthy Lifestyle

- Regular physical exercise
- Cognitive leisure activities
- Socialization
- Mediterranean diet: https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/expert-answers/alzheimers-disease/faq-20058062

  MIND Diet: https://www.nih.gov/news-events/nih-research-matters/healthful-diet-linked-reduced-risk-cognitive-decline
- Encourage smoking cessation
- ETOH limitation
- Adequate sleep
- Stress and anxiety reduction

Risk Factor Management

- BP lowering for hypertensive individuals.
  - Avoid aggressive blood pressure lowering (can compromise cerebral perfusion).
- Management of hyperlipidemia (follow established norms).
- Diabetes management
  - Follow established recommendations for glucose control to prevent complications, including cognitive decline associated with diabetes.
  - Use caution as hypoglycemia can also pose risk in the elderly.
- Follow established norms for primary stroke prevention or secondary stroke prevention (in those with history of stroke).

Medication Strategies

Pharmacologic interventions include AD symptomatic therapies, medications for neuropsychiatric symptoms, optimizing medications that impact cognitive reserve, and disease- modifying therapies (for early-stage Alzheimer's disease).

- **Eliminate any medications with potential negative cognitive impact and avoid polypharmacy** (as per Beers criteria).
  - Avoid the following drugs in dementia or cognitive impairment due to adverse CNS effects
    - Anticholinergics
    - Benzodiazepines
    - Z drugs for insomnia (zolpidem, zaleplon, eszopiclone)
    - Antipsychotics (associated with increased mortality risk in elderly dementia patients, mostly due to cardiovascular or infections events); avoid unless nonpharmacologic options have failed or there is concern for patient/caregiver safety.
    - Avoid using antimuscarinic medications (atropine, scopolamine, glycopyrrolate, ipratropium bromide) in patients taking acetylcholinesterase inhibitors (ACHEIs).

- **Start acetylcholinesterase inhibitor (***except in Frontotemporal Dementia, see below)** (if no contraindications, e.g. significant bradycardia, sick sinus syndrome/cardiac conduction defects, gastrointestinal bleeding or ulcer, bladder obstruction, caution if seizure disorder, asthma or Chronic Obstructive Pulmonary Disease (COPD).
  **see algorithm for ACHEI initiation and management

- **Memantine can be added for progression or prominent Alzheimer's Disease symptoms** (clinically indicated in middle to late stage disease, except in Frontotemporal Dementia, see below).
  **see algorithm for Memantine initiation and management
  - Has also been shown to decrease neuropsychiatric features such as agitation and disinhibition.

- Consider referral for disease modifying therapies (amyloid monoclonal antibody medications: donanemab or lecanemab) for the treatment of Alzheimer's disease in patients with **MCI** or **mild** dementia stage of disease who have positive confirmatory AD biomarkers (amyloid brain PET or CSF AD profiles ß-amyloid, total tau, phosphor-tau). **More impaired patients and those with other primary pathologies (e.g. Lewy Body or FTD) do not benefit from these therapies.** APOE genotyping should be ordered to help with risk stratification for amyloid mAb treatment. The risk benefit and choice of amyloid mAb will need to be individualized for each patient. Conventional management of AD clinical symptoms should also continue.
  ***See Table 3, Criteria for Amyloid Monoclonal Antibody

- ***Treatment of Frontotemporal Dementia** should begin by defining relevant signs and symptoms that are impairing quality of life in order to develop an individualized therapeutic strategy with maximal chances for success.
  - Consider SSRIs as a first line therapy, especially in behavioral variant Frontotemporal Dementia.

- If delusional consider treatment with an antipsychotic.
- The use of acetylcholinesterase inhibitors and memantine are not supported by the data and therefore should not be used in the treatment of Frontotemporal Dementia. The exception is where there is uncertainty about whether the patient has Frontotemporal Dementia or Alzheimer's Disease; in such cases, a therapeutic trial of a cholinesterase inhibitor is reasonable.

  **see algorithm for ACHEI & memantine initiation and management

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Acetylcholinesterase Inhibitors (ACHEIs) Initiation and Management

Indications for Use

- Three acetylcholinesterase inhibitors (ACHEIs) (Donepezil (Aricept), Galantamine (Razadyne), and Rivastigmine (Exelon) are FDA approved medications for the treatment of Alzheimer's Disease .
- ACHEIs have also shown benefit in Vascular Dementia (because of the evidence of cholinergic dysfunction in Vascular Dementia and high prevalence of comorbid Alzheimer's Disease).
- ACHEIs have also shown benefit in Lewy Body Dementia (because of the marked decrease in cholinergic functioning in Lewy Body Dementia patients). Rivastigmine also has a Parkinson's Dementia FDA label.
    - ACHEIs may also have greater potential for improvement in Lewy Body Dementia than Alzheimer's Disease and treatments with ACHEIs may improve various neuropsychiatric symptoms, especially in Lewy Body Dementia.

Efficacy & Tolerability

- **Efficacy:** All three ACHEIs have demonstrated clinical benefits on cognitive function, global clinical status, and performance of activities of daily living. There are no proven clinically meaningful differences between the agents in terms of efficacy. Tolerability and efficacy are dose dependent.
- **Tolerability:** All three agents have similar tolerability profiles.
- **Contraindications:** Significant bradycardia, sick sinus syndrome/cardiac conduction defects, gastrointestinal bleeding or ulcer, bladder obstruction; caution if seizure disorder, asthma or Chronic Obstructive Pulmonary Disease (COPD).
- **Most Common Side Effects:** Nausea, vomiting and diarrhea, urinary incontinence, weight loss, skin irritation (with Rivastigmine patch).
- **Other Common Side Effects:** Vivid dreams (particularly with Donepezil) and leg cramps. Anecdotally, Rivastigmine capsules appear to have the most problematic side effects.

Initiation and Management

- **Diagnosis of Alzheimer's Disease, Lewy Body Dementia, or Vascular Dementia:** Start AChEI (if no contraindications, e.g. significant bradycardia, sick sinus syndrome/cardiac conduction defects, gastrointestinal bleeding or ulcer, bladder obstruction, caution if seizure disorder, asthma or Chronic Obstructive Pulmonary Disease).
  - Begin with Donepezil (oral), Galantamine (oral), or Rivastigmine (oral or transdermal, *note that oral Rivastigmine historically has the most severe gastrointestinal side effects).
    - Choice dependent upon caregiver preference of modality (oral vs transdermal), ease of use, tolerability based on past history, cost (dependent on insurance coverage—all generic but price varies greatly by plan).
    - Typically Donepezil is preferred tier 1 on most plans.
  - Start with the lowest dose and titrate up to highest tolerated dose. (see attached table 1 for dosing titration instructions)
  - A 23 mg non-crushable tablet of Donepezil is available, but evidence does not support a clinically important advantage to the higher dose, and it is associated with increased side effects (particularly gastrointestinal side effects).

- **Tolerability Issues**
  - If gastrointestinal side effects, switch to Rivastigmine patch or alternate oral agent if cost is an issue with the patch.
  - With Donepezil, consider morning dosing in patients that have vivid dreams or new nighttime behaviors/activation.
  - If rash with patch, switch to oral agent.
  - Use caution if prescribing oral Rivastigmine given high rate of gastrointestinal side effects.
  - If patient develops new urinary incontinence after initiation of AChEI, consider changing dose or weaning before prescribing Antimuscarinic.

- **Ongoing Therapy**
  - Continue AChEI throughout disease course unless signs of intolerability emerge or at end stage disease when patient has lost all meaningful function and is free of behavioral symptoms.
  - If behavioral symptoms emerge as disease progresses, consider weaning AChEI before adding medication for behavioral symptoms because AChEIs can be too activating in some patients.

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Memantine (Namenda) Initiation and Management

Initiation and Management

- **Diagnosis of Alzheimer's Disease, Lewy Body Dementia, or Vascular Dementia:** Memantine is FDA approved for moderate to severe dementia. Consider initiation of Memantine with progression to moderate stage disease OR if there are new neuropsychiatric features, consider the addition of Memantine.
    - Continue on ACHEI medication and add memantine.
    - Start Memantine at 5 mg qAM and titrate up to goal dose of 10 mg BID if on immediate release form or start at 7 mg XR qday and titrate up to goal dose of 28 mg per day XR formulation.
    - Use titration kit for first month or titrate up as follows:
        - Immediate release: 5 mg daily x 1 week then 5 mg BID x 1 week then 5 mg qAM and 10 mg qpm x 1 week then 10 mg BID thereafter OR
        - Extended Release: 7 mg XR daily x 1 week then 14 mg XR daily x 1 week then 21 mg XR daily x 1 week then 28 mg XR daily thereafter .
    - Common side effects: headache, dizziness, increased confusion, depression or agitation, somnolence, constipation, hallucinations.

- **Ongoing therapy**
    - Continue Memantine throughout disease course unless signs of intolerability emerge or at end stage disease when patient has lost all meaningful function and is free of behavioral symptoms.
    - If behavioral symptoms emerge as disease progresses, consider weaning Memantine before adding medication for behavioral symptoms as it can cause agitation and behavioral symptoms in some patients.

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Targeted Management of Common Symptoms of Dementia

Depression and Anxiety

- Patients with dementia may develop apathy, sleep impairment, and social withdrawal. These symptoms may suggest the presence of depression but may also be a consequence of their cognitive impairment. Patients may also become depressed in reaction to slipping mental capacity or as a direct biologic consequence of the underlying neurologic disorder.

- Few studies guide selection of antidepressant medications in dementia but SSRIs are the preferred starting point (avoid ricyclic antidepressants because of anticholinergic effects).

- Selection of a specific SSRI is generally based upon the side effect profile, drug interactions, targeted symptoms, and cost. Note that there is an increased risk of hyponatremia in patients on SSRIs, specifically if combined with diuretics. Use with caution and check labs after starting therapy.

- Sertraline (Zoloft) and Escitalopram (Lexapro) or Citalopram (Celexa) (not to exceed 20 mg in older adults, caution re: QT prolongation risk) are commonly used. Fluoxetine (Prozac) can also be helpful if a more activating option is needed but use with caution because of long half- life and multidrug interactions. Duloxetine can be helpful if there is a coexisting pain component.

- Paroxetine (Paxil) (because of anticholinergic properties) is the LEAST desirable SSRI in dementia.

- The atypical antidepressants such as Venlafaxine (Effexor) and Bupropion (Wellbutrin) may also be effective but have not been well studied in Alzheimer's Disease. Both are beneficial if more activation is needed but caution re: risk of elevated blood pressure with Venlafaxine.

Neuropsychiatric/Behavioral Symptoms

(Delusions, Hallucinations, Paranoia, Agitation, Aggression, Apathy, Disinhibition)

- Neuropsychiatric symptoms are common in dementia but may be under-reported. **Clinicians should regularly inquire about delusions, hallucinations, paranoia, agitation, aggression, apathy, and disinhibition at each visit.**

- **Identifying the genesis of the abnormal behavior** is critical to effective management. Unmet needs (food, water, etc.), a concomitant medical illness, uncontrolled pain, sleep disturbance, medication toxicity, and other causes of delirium should be considered and ruled out whenever new behavioral disturbances arise. If no cause for delirium found, consider disease progression.

- **Treating underlying causes of behavioral symptoms and a focus on nonpharmacologic interventions such as structured stimulating activities, exercise, sleep hygiene, reassurance, and redirection** (see Table 2 below) is ideal in this population. If psychotic symptoms are not bothersome to the patient and are not placing others at risk, pharmacologic treatment is not necessary.

- If pharmacologic intervention is indicated (due to failure of non-pharm strategies or behaviors having negative impact on quality of life or there is a risk to patient/caregiver safety), **pharmacologic interventions may be indicated:**
  - Start with a cholinesterase inhibitor in patients who are not already on one due to some evidence of efficacy in treating behavioral symptoms of dementia.
  - Memantine may also be considered in moderate to late stages (some studies show that treatment with Memantine may reduce agitation/aggression, irritability, and other behavioral disturbances); be mindful that it can also increase confusion and mood disturbance as well.
  - If patient is already on a cholinesterase inhibitor or Memantine, consider weaning off one or both of these as they can be activating or cause behavioral symptoms in some instances but monitor for cognitive decline.

- **Selective serotonin reuptake inhibitors (SSRIs)**, have been shown to be useful in the management of agitation and paranoia in patients with Alzheimer's Disease, as the symptoms are often driven by a mood disorder that is poorly verbalized. *Note: avoid use of Paroxetine (Paxil) due to its anticholinergic properties.

- As an alternative, **trazodone** (starting dose 25 mg at bedtime, consider slow up titration) is well tolerated and is often used for sleep onset and to treat behavioral symptoms in patients with dementia.

- **Mood stabilizing drugs** have also been used with mixed results and side effect concerns. Lamotrigine (Lamictal) is the preferred first choice (be mindful of need for slow titration and risk of rash including Stevens-Johnson's Syndrome).
    - **Other options include:** Divalproex Sodium (Depakote) and Carbamazepine (Tegretol) but they have more worrisome side effect profiles.

- **Atypical neuroleptics -** may increase mortality and are not approved for the treatment of behavioral disorders in patients with dementia by the FDA. They should not be used routinely to treat neuro psychiatric symptoms of dementia. However, their **benefits often still outweigh their risks in patients with dementia when treatment of psychotic symptoms including hallucinations, paranoia, and delusions is critical to patient and caregiver safety, wellbeing, and quality of life. *Inform the patients and families of the potential risks, including increased mortality.**

    - **Quetiapine (Seroquel)** – tends to have least amount of parkinsonian and cognitive side effects and can be titrated up from 25 mg with large dosing range. It is the weakest of the antipsychotics so higher doses may be needed to manage more severe psychotic symptoms or patient may need to be switched to another antipsychotic (Risperidone or Olanzapine). Quetiapine can cause increased sedation but should never be used solely to help with sleep.

    - **Risperidone (Risperdal) and Olanzapine (Zyprexa)** have also been used but caution due to risk of extrapyramidal symptoms and metabolic side effects (e.g., weight gain, diabetes, and hypercholesterolemia). Start with low doses and slowly titrate up until symptoms are managed.

    - **Pimavanserin (Nuplazid)** is a newer alternative antipsychotic agent with some limited evidence of efficacy in this setting; it is typically started at 34 mg daily. Cost/insurance coverage may be a barrier.

Sleep Disturbances

- **Sleep disturbances and disorders** are important to recognize and treat in patients with dementia, **as they are a major contributor to caregiver distress and are associated with an increased likelihood of institutionalization.**

- **Multiple contributing factors** — age- and dementia-related changes in sleep and circadian rhythms, primary sleep disorders, institutional and environmental factors, and comorbid illnesses and medications.

- **The best way to detect and diagnose sleep-wake disturbances in patients with dementia is to routinely ask about them.** Caregiver or bed partner interview is crucial. Presenting sleep symptoms include:

- Difficulty falling or staying asleep
- Abnormal movements or behaviors during sleep (restless leg syndrome, periodic limb movements, REM Behavior Disorder)
- Abnormal breathing patterns (e.g. Obstructive Sleep Apnea)
- Excessive Daytime Sleepiness

- Many sleep-wake disorders are diagnosed by history alone but **some require further diagnostic tools or formal sleep testing:**
  - Sleep diary and/or actigraphy (a noninvasive technique to measure sleep quality using a wristwatch style actigraph) for the evaluation of sleep-wake patterns and the diagnosis of circadian sleep-wake rhythm disorders.
  - Polysomnography for the diagnosis of REM behavior disorder, obstructive sleep apnea, or periodic limb movement disorder.

- **In managing sleep disturbances, initial focus should be on nonpharmacologic interventions to include:**
  - Environmental restructuring.
  - Management of polypharmacy (antipsychotic medications, stimulants, respiratory medications, antihypertensives, and decongestants may significantly impact sleep and result in sleep disturbances; timing of medication administration should be considered, such that stimulating medications and diuretics are taken earlier in the day and sedating medications are administered prior to bedtime).
  - Sleep hygiene education.
  - Stabilization and maintenance of consistent sleep-wake schedules.
  - Stimulus control (e.g. avoiding naps, using bed for sleep and sex only).
  - Caffeine and alcohol cessation.

- **Pharmacologic treatment:**
  - **Precautions:** A National Institutes of Health expert panel concluded that there is **no systematic evidence for the effectiveness** of antihistamines, antidepressants, anticonvulsants, or antipsychotics (e.g., quetiapine) for the treatment of insomnia, and that **these drugs are associated with more risks than benefits in the treatment of insomnia, particularly in older persons.**
  - **Nonbenzodiazepine benzodiazepine receptor agonists (e.g., zolpidem) are not recommended in dementia and are associated with risks that are similar to or greater than those of benzodiazepines.**
  - **Pharmacotherapy for insomnia is poorly studied in patients with dementia and is associated with a high risk of side effects.** Options to try include **melatonin (up to 10 mg qhs), trazodone, and ramelteon**, however, none have shown to have a positive impact on sleep outcomes in dementia. Recognize that melatonin is a supplement and formulations can vary in strength and efficacy.

- CPAP has been shown to improve sleep and have some positive impact on cognition in patients with dementia. While some patients may not tolerate it, it should be considered in patients with mild to moderate dementia and comorbid OSA.

- Rapid eye movement, sleep behavior disorder, and restless leg syndrome occur with increased frequency in patients with dementia and are readily treatable with nonpharmacologic and pharmacologic therapies.
    - Recommended treatments:
        - **Dopamine agonist (e.g. Ropinirole) for restless leg syndrome or periodic limb movement disorder.**
        - **Melatonin or low-dose Clonazepam for rapid eye movement sleep behavior disorder with potentially injurious behaviors.**

Lewy Body Dementia

Motor Symptoms/Parkinsonism

(Parkinsonism including bradykinesia, rigidity, tremor, gait disturbance, retropulsion, hypomimia [facial masking], etc.)

- Begin with **daily exercise, consider physical therapy (LSVT BIG program (physical therapy program for PD) for motor and LSVT Loud program (speech therapy program for PD).**
  - Find certified clinicians here: https://www.lsvtglobal.com/

- **If motor symptoms are functionally limiting**, consider the addition of **carbidopa/levodopa (Sinemet).**
  - Use caution and consider **risk of exacerbating psychotic symptoms (particularly hallucinations, delusions) and confusion**; also monitor for common side effects including dizziness, gastrointestinal symptoms, dyskinesia (uncontrolled, involuntary movements).
  - **Start low and titrate slowly** (e.g. begin with carbidopa/levodopa 25/100 mg tabs- give tab po BID to begin and titrate up by or 1 tab per week to a goal of 1 tab TID over several weeks).
    - Better absorption on empty stomach but give with food if patient experiences nausea.
    - Give doses while awake and moving (e.g. upon arising, before lunch, and before dinner).
  - **Patients with Lewy Body Dementia show a lower response than those with Parkinson's Disease**, and it has been suggested that this may be a distinguishing diagnostic feature.
  - If no improvement noted in motor symptoms at 1 tab TID of carbidopa/levodopa, consider further upward titration as tolerated to max of 3 tabs (25/100) po TID.
  - **If no improvement noted 3 tabs TID of carbidopa/levodopa, consider tapering off as patient is unlikely to receive benefit at higher doses (avoid abrupt cessation).**

Autonomic Dysfunction

- **Autonomic dysfunction is a commonly seen feature** of LBD. If there are clinically significant manifestations of orthostasis or autonomic dysfunction (lightheaded, dizzy, frequent "spells", persistent fatigue, unexplained falls), treatment may be indicated. **If pt has frequent syncopal spells, a referral to cardiology may also be indicated.**

- If pt is orthostatic and/or showing signs of autonomic dysfunction-
  - **Eliminate offending medications** (antihypertensives, other meds that potentially lower BP)
  - **Ensure proper hydration**
  - **Consider use of ankle pumps and compression stockings**

- If these measures are ineffective, **fludrocortisone (Florinef) and/or midodrine (ProAmatine) may be tried** (start low and slowly titrate as needed and have patient/family keep blood pressure and heart rate log including early morning, supine blood pressure [before arising from bed]).

Neuropsychiatric Features

(delusions, hallucinations, paranoia, agitation)

- Psychotic symptoms including **hallucinations, delusions, and paranoia are common in Lewy Body Dementia** and can be very difficult to manage.
  - Hallucinations are a common feature of DLB. Normalizing this symptom and coaching family on how to talk about the hallucinations can be helpful (e.g. acknowledging them as a reality of their disease can be helpful for some. For others, 'playing along' and then redirecting can be helpful. A general rule of thumb is to not argue and to try and reassure and redirect).
  - **Nonpharmacologic behavioral interventions are recommended** and caregiver education on how to respond to behavioral symptoms is critical.
  - Hallucinations only require treatment if they are distressing or disturbing/impacting quality of life or safety or disrupting sleep. **Some patients learn to live with them and do not need treatment.**
  - Psychotic symptoms may improve with ACHEIs (donepezil, galantamine, rivastigmine). **If patient has not yet been treated with an ACHEI, this should be the first line of therapy for psychosis in LBD.**
  - If the symptoms are refractory to ACHEI treatment and behavioral interventions **and if symptoms cause significant impairment and impact safety of caregivers, antipsychotics such as Quetiapine (Seroquel) (begin with 12.5 mg qhs) can be used** in lower doses with caution and attention to neuroleptic sensitivity.
    - **Quetiapine is the least likely to cause extrapyramidal side effects** but it is also the least effective of the antipsychotics. **If ineffective, consider very low dose Risperidone or Olanzapine.**
  - When considering the addition of an antipsychotic, **a careful discussion with family members about the risk of neuroleptic sensitivity as well as the US Food and Drug Administration black box warning (increased risk of cardiovascular mortality) regarding use of these medications in patients with dementia is necessary.**
  - **The newest antipsychotic** that has been FDA approved for psychosis in Parkinson's disease is **Pimavanserin (Nuplazid)**.T his may be a consideration if covered by insurance **in the event that patient does not respond to the above interventions.**

Sleep Disturbances/REM Behavior Disorder

- REM behavior disorder can cause patients with Lewy Body Dementia to act out their dreams and may pose a safety risk to themselves or their bed partners.
  - **Withdraw or reduce drugs potentially causing sleep behavioral disorder**, such as monoamine oxidase inhibitors, antidepressants, beta blockers (Bisoprolol), opioids (Tramadol), and centrally acting alpha-agonist hypotensive agents (Clonidine).
  - Counsel patient and bed partner to **establish a safe sleeping environment and injury prevention** - remove dangerous objects next to bed, pillow, or mattress on floor; bed partner to sleep in different room or bed.
  - **Treatment is indicated if sleep behavioral disorder disrupts sleep or if behavior poses a safety risk to patient or bed partner:**
    - Begin with **low doses of Melatonin** (3 to 5 mg) and titrate up to 10 mg. Give 1-2 hours before bedtime and consider long acting formulation.
    - **If Melatonin is ineffective, try Clonazepam (Klonopin) (**0.25 to 1.5 mg) given at bedtime. Melatonin is preferred as initial therapy in the setting of cognitive impairment due to lower risk of side effects.
    - **Pramipexole (Mirapex) and Ropinirole (Requip)** are also reasonable alternatives.

Medication Sensitivity and Acute Metabolic/Infectious Events

- **Patients with Lewy Body Dementia are generally much more sensitive to medication effects and to metabolic and infectious events.** Something as minor as **dehydration can result in severe confusion and changes in mobility** and patient should be assessed for metabolic disturbance or infection any time there is an acute change in behavior or physical status. Fluctuations in cognition and motor symptoms are also very common in Lewy Body Dementia and may occur without any identifiable cause.

- Attempts should also be made to **avoid polypharmacy and to limit or avoid exposure to the following drug classes:**
  - **Anticholinergic medications should be avoided** as they can exacerbate the symptoms of dementia.
  - **Traditional antipsychotic medications can precipitate severe reactions and may double or triple the rate of mortality** in patients who have dementia with Lewy bodies.
  - **Benzodiazepines should also be avoided** due to increased risk of sedation and impaired mobility and falls.

Frontotemporal Dementia - Behavioral Variant FTD, Language Variant FTD (Primary Progressive Aphasia), Progressive Supranuclear Palsy, Corticobasal Degeneration, FTD/ALS

Behavioral Changes **(Disinhibition, impulsivity, abnormal eating behaviors [unusual food preferences, food seeking behavior binge eating, or eating non-food items], withdrawal/apathy)**

Neuropsychiatric Features **(Delusions hallucinations paranoia)**

- **Behavioral symptoms arise early in bv FTD but may be problematic in the other subtypes** and contribute substantively to the care burden of patients with FTD. These **can be quite challenging to treat.**

- **Nonpharmacologic interventions are important** and include:
  - Exercise program; modification of the home environment; increased supervision; physical therapy, occupational therapy, speech therapy; behavioral modification techniques; and caregiver support and respite.
  - For disinhibited behavior in public, awareness cards can be a helpful caregiver tool (https://www.theaftd.org/living-with-ftd/resources/awareness-cards/).

- **A treatment trial of an SSRI (e.g., Escitalopram (Lexapro) 10 - 20 mg qday or Sertraline (Zoloft) 50 - 200 mg qday) or Trazodone (25 - 150 mg qday) is suggested as initial pharmacotherapy** for troubling behavioral symptoms of FTD.
  - **SSRIs most effective for** disinhibition, anxiety, impulsivity, repetitive behaviors, sleep difficulties, and eating disorders.
  - **Trazodone most effective for** irritability, agitation, depressive symptoms, and eating disorders.

- Medications **may exacerbate behavioral symptoms, slow movement, and reaction times, and cause cognitive deterioration.**
  - Continuously reevaluate the role of the medications and consider tapering.

- **Atypical antipsychotic medications can help with psychotic symptoms in FTD.**
  - Because of adverse effects and increased risk of mortality, antipsychotic medications **should**

be considered a last resort only after trying behavioral modifications and SSRIs.

- Patients with FTD are particularly vulnerable to the extrapyramidal side effects of antipsychotics.
- If multiple trials of SSRIs do not help behavioral symptoms, **low-dose quetiapine (Seroquel) (eg, 12.5 mg starting dose) may be added** and titrated slowly as needed (less likely to cause EPS side effects).

- **Alzheimer's Disease symptomatic therapies are typically not recommended for patients with Frontotemporal Dementia** (exception: if cognitive deficits are primary, then cautiously consider a trial), (see Acetylcholinesterase inhibitors and emantine guidelines above).

Language Deficits

- **Speech therapy and the use of communication aids may provide benefit early on in patients with language variants of frontotemporal dementia.**

- Later in the course of the illness, **evaluation of swallowing may be needed to understand aspiration risk.**

Motor Symptoms

(Specifically in Corticobasal Degeneration and Progressive Supranuclear Palsy)

- **Patients with Frontotemporal Dementia who have parkinsonism (usually those with Corticobasal Degeneration and Progressive Supranuclear Palsy) typically do not respond to dopaminergic medications** such as Levodopa or Amantadine, although some patients have transient motor improvements on these medications.
  - **Psychosis and vivid dreaming can be limiting side effects.**
  - Patients **may receive a treatment trial of levodopa-carbidopa**, although response to this medication may be minimal or transient (see titration above under Lewy Body Dementia).

- In Coricobasal Degeneration and Progressive Supranuclear Palsy **medications that can be used for management of tremor** include Propranolol, Clonazepam, Gabapentin, Topiramate, and Primidone.

- **Baclofen and anticholinergics may be useful for rigidity and dystonia, and Clonazepam is helpful in some cases for myoclonus.**

- **Botulinum toxin has been reported to provide some relief of dystonic spasms and pain in the limbs.**
  - Unfortunately, the efficacy of these treatment agents is low.

Tables

Table 1

Cholinesterase Inhibitors Used for Treatment of Dementia Dose and Administration

Drug	Formulations	Starting Dose	Maintenance Dose	Comments
Donepezil	Tablet or oral disintegrating tablet	5 mg orally, once daily	10 mg daily (increased after 4 to 6 weeks)	
Galantamine	Immediate-release tablet or solution	4 mg orally, twice daily	12 mg twice daily (increased in monthly intervals by 4 mg twice-daily increments	Give with meals. Maximum 8 mg twice daily with moderate renal or liver impairment. Do not use with severe renal or liver impairment.
	Extended-release capsule	8 mg orally, once daily	24 mg once daily (increased in monthly intervals by 8 mg once-daily increments)	Maximum 12 mg once daily with moderate renal or liver impairment. Do not use with severe renal or liver impairment.
Rivastigmine	Capsule	1.5 mg orally, twice daily	6 mg twice daily (increased in 2- to 4-week intervals by 1.5 mg twice-daily increments)	Give with meals. Slow and cautious titration with renal or liver impairment or low body weight.
	Transdermal patch	4.6 mg/24 hours	9.5 to 13.3 mg/24 hours (increased in monthly intervals by 4.6 mg increments)	Can cause rash; rotate sites. Fewer side effects than capsule. Maximum dose 4.6 mg/24 hours with mild to moderate liver impairment or low body weight. Do not use with severe liver impairment.

Graphic 63284 Version2.0

Table 2

Nonpharmacologic Approaches toManage Common Behavioral Symptoms and Mood Disorders

Behavioral Symptom	Nonpharmacological Intervention
Apathy	Stimulation/activities • Simple tasks
Sleep Disturbances	Take steps to maintain regular, good quality sleep • Stimulation during the day (especially adult day service) • Reduction in excessive stimulation/noise in the evening
Irritability/Agitation	Break down tasks into simple steps • Redirection
Wandering	Visual cues • Exercise • Safe places to wander • Enrollment in wandering assistance schemes
Mood Disorders Psychotic Disorders	Exercise Reassurance • Distraction rather than confrontation • Removal of potential sources of confusion, e.g. mirrors
Eating/Appetite Disorders	Offering simple, finger foods • Removal of distractions from dining area • Soothing music

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369281/

Table 3

Criteria for Amyloid Monoclonal Antibody

Box 1: Criteria for Amyloid Monoclonal Antibody[1,2,85,86]
• Confirmed diagnosis of mild Alzheimer's disease (AD) (mild cognitive impairment [MCI] or mild dementia with positive amyloid brain PET or cerebrospinal fluid [CSF] ß-amyloid, total tau, phospho-tau profile; plasma tau assays not considered confirmatory at the time of this publication). • Age: 60 to 85 (donanemab); 50 to 90 (lecanemab). • Objective measurement of cognitive decline (MMSE≥22, MOCA≥16)[46, 47]; functional questionnaire to augment discussion (FAQ)[52]; some Center for Medicare Services payors require Clinical Dementia Rating. • MRI brain without exclusion (greater than 4 microhemorrhages; superficial siderosis (lecanemab trial did not allow; donanemab trial; allowed 1 area); other vascular malformation or lesion that could increase risk of bleeding; prior macrohemorrhage > 1cm). • Baseline lab work without significant abnormality, especially coagulation factors and platelets. • Apolipoprotein E genotype to help inform risk/benefit discussion. • Agrees to safety monitoring with MRI scans. • Care partner or agent to assist with infusion and safety monitoring process. • Absence of other exclusionary criteria (see text and detailed list in Cummings and colleagues). [88]

References

Cummings JL, Isaacson RS, Schmitt FA, Velting DM. A Practical Algorithm for Managing Alzheimer's Disease: What, When, and Why?*Annals of Clinical and Translational Neurology* . 2015;2(3):307-323. doi:10.1002/acn3.166.

Press, D, & Alexander, M (2021). Management of Neuropsychiatric Symptoms of Dementia.*UpToDate* . Retrieved Jan 12, 2022 from https://www.uptodate.com/contents/management-of-neuropsychiatric-symptoms-of-dementia?topicRef=5086&source=see_link

McFarland, N (2021). Prognosis and Treatment of Dementia with Lewy Bodies.*UpToDate* . Retrieved Jan 20, 2022 from https://www.uptodate.com/contents/prognosis-and-treatment-of-dementia-with-lewy-bodies?search=lewy%20body%20dementia&source=search_result&selectedTitle=2~119&usage_type=default&display_rank=2

Lee, S (2019). Frontotemporal Dementia Treatment.*UpToDate* . Retrieved March, 17, 2022 from https://www.uptodate.com/contents/frontotemporal-dementia-treatment?search=frontotemporal%20dementia&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

Smith, E, & Wright, C (2020). Treatment of Vascular Cognitive Impairment and Dementia.*UpToDate* . Retrieved March 17, 2022 from https://www.uptodate.com/contents/treatment-of-vascular-cognitive-impairment-and-de- mentia?search=vascular%20dementia&source=search_result&selectedTitle=2~61&usage_type=default&dis- play_rank=2

Rabinovici G. D. (2019). Late-onset Alzheimer Disease.*Continuum (Minneapolis, Minn.),* 25(1), 14–33. https://doi.org/10.1212/CON.0000000000000700

Mendez M. F. (2019). Early-onset Alzheimer Disease and Its Variants.*Continuum (Minneapolis, Minn.)* , 25(1), 34–51. https://doi.org/10.1212/CON.0000000000000687

Hales, C.M. (2025). Alzheimer's Disease Diagnosis and Management in the Age of Amyloid Monoclonal Antibodies*Medical Clinics of North America,* 109 (2), 463-483.

Cummings J. Anti-amyloid monoclonal antibodies are transformative treatments that redefine Alzheimer's disease therapeutics. Drugs 2023;83(7):569–76.

https://www.theaftd.org/living-with-ftd/resources/awareness-cards/

https://www.lsvtglobal.com/

https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/expert-answers/alzheimers-prevention/faq-20058140

https://www.nih.gov/news-events/nih-research-matters/healthful-diet-linked-reduced-risk-cognitive-decline