Dementia

Neurological changes of “Normal” brain aging

Successful aging can be viewed as either a state of being that is objectively measured (public health perspective) or ones’ view of a process of continuous adaptation to physical limitation. Which one should we consider as the gold standard? In individuals older than 85 years, perhaps only 2% are free of common age-associated diseases. In one survey, only 10% fit the usual public health perspective of “successful aged”, yet 45% of that sample rated their health as good to excellent. Cognition consists of memory, language, visuospatial and executive functions.

Beginning in young adulthood, predictable changes occur and characterize all aging brains:
- Loss of brain volume, esp. in the hippocampus and frontal lobes as well as neuron loss (10% of the 20 billion neocortical neurons by the age of 90), but not uniformly and hippocampal loss is minimal
- Loss of myelinated nerve fibers, loss of synapses and the dendritic arbor
- Cytoskeletal changes, neurofibrillary tangles, deposition of amyloid in brain and blood vessels
- (Accumulate infarcts)

Signs of Dementia Compared with Typical Age-Related Changes

<table>
<thead>
<tr>
<th>Signs of Dementia</th>
<th>Typical Age-Related Changes</th>
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<tbody>
<tr>
<td>Memory loss that disrupts daily life</td>
<td>Sometimes forgetting names or appointments, but remembering them later</td>
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<tr>
<td>Challenges in planning or solving problems</td>
<td>Making occasional errors when balancing a checkbook</td>
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<td>Difficulty completing familiar tasks at home, at work or at leisure</td>
<td>Occasionally needing help to use the settings on a microwave or record a television show</td>
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<tr>
<td>Confusion with time or place</td>
<td>Getting confused about the day of the week but figuring it out later</td>
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<tr>
<td>Trouble understanding visual images and spatial relationships</td>
<td>Vision changes related to cataracts, glaucoma or age-related macular degeneration.</td>
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<tr>
<td>New problems with words in speaking or writing</td>
<td>Sometimes having trouble finding the right word</td>
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<tr>
<td>Misplacing things and losing the ability to retrace steps</td>
<td>Misplacing things from time to time and retracing steps to find them</td>
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<tr>
<td>Decreased or poor judgment</td>
<td>Making a bad decision occasionally</td>
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<tr>
<td>Withdrawal from work or social activities</td>
<td>Sometimes feeling weary of work, family and social obligations</td>
</tr>
<tr>
<td>Changes in mood and personality</td>
<td>Developing very specific ways of doing things and becoming irritable when a routine is disrupted.</td>
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Demographics of cognitive impairment

- **Alzheimer disease (AD)** may account for **up to 60-80%** of all cases of dementia. Dementia with Lewy bodies may be the third most common etiology.

- **AD is the most common cause of dementia** among people 65 years or older

- **AD is the sixth leading cause of death**

- It is estimated that there are **5.4 million people with dementia in the U.S. (the majority have AD and 2/3 are women)** and by 2050 it will increase to 14-16 million. Delaying the onset of AD by five years would reduce the prevalence by one-half!

- **The incidence and prevalence of AD rise exponentially from 15% in people aged 65 to 74 to almost 1/3rd of those older than 85 years**, but what is the number of the undiagnosed (is the incidence decreasing as other medical conditions are treated, i.e. HTN?).

- Direct and indirect payments for care of AD individuals is estimated at $236 billion/year (similar direct healthcare expenditures as heart disease or cancer); estimated value of unpaid caregiver assistance is estimated to be $221 billion/year.

**Primary risk factors**

- Age
- Family history
- Genetic (APOE ε4, trisomy 21)

**Modifiable factors to reduce the risk of Alzheimer’s disease (currently the evidence is insufficient)**

- Observational studies - Population attributable risk (relationship of prevalence and association): physical inactivity, depression, mid-life obesity, mid-life HTN, DM and smoking (a role for cognitive inactivity?). If all 7 were reduced by 10-25%, potentially prevent 184,000 to 492,000 cases of dementia in the U.S.

- **No clear benefit**: regular consumption of omega-3 fatty acids, Vit B12, NSAID, Vit E, Gingko Biloba, antibiotics (rifampin and doxycycline?), statins (absence of lipid disorder) and estrogen.

**Diagnostic strategies to assess cognitive impairment**

- **Approach to the patient**: Patient evaluation is “global” (issues seldom limited to behavior or memory); knowledge of cardinal symptom may help clinician classify disorder; nature of onset may indicate whether symptoms have vascular, subacute, or chronic neurodegenerative etiology.

- **Symptoms**: Ask about the course of the symptoms (e.g., fluctuating symptoms may be associated with seizures or Lewy bodies, longer duration of symptoms increases the likelihood of neurodegenerative process and an interruption of expected chronology may indicate secondary pathology). The clinician should assess how signs and symptoms affect daily activities to determine whether the patient has dementia versus mild cognitive impairment. For example, early amnestic component followed by deficits in executive function, language, and decision-making suggests Alzheimer disease. If the patient initially becomes apathetic or more outgoing, then displays changes in behavior and language, the clinician should consider a frontotemporal disorder. Medications are reviewed to determine whether any have potential to contribute to impairment and smoking, drinking, or using illicit drugs may exacerbate the process.

- **Bedside mental status examination**: Standardized approaches include, e.g., *Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE)*; however, when test results do not correlate with the presentation, some relevant history may have been missed; clinician must consider whether the instrument used appropriately for evaluating symptoms.

- **Taking the history**: Begin by questioning the patient to assess their insight into the problem; if the patient has minimal insight, the clinician should ask patient’s permission to speak with caregiver or
informant who accompanies patient; in most cases, adequate history reveals diagnosis or differential diagnosis.

- **Pointers for evaluation:** History helps to determine which instrument most likely to be informative. During testing, note the areas where the patient performs poorly and nature of responses or errors. For example, a patient who cannot draw a clock may be unable to plan drawing, write numbers, or understand where hands of the clock should be placed to indicate time, each of which may represent impairment of different cognitive domains. The clinician should assess whether the greatest difficulty is language, executive function, attention, or visuospatial domain.

- **Choosing instruments:** **MoCA is a good initial screening test** for impaired patients but too difficult for those with severe impairments. Other instruments are used if results of testing do not match clinical suspicion. Examples include the Trail Making Test Part B, Multilingual Naming Test, and the Boston Naming Test. The MMSE (from Folstein and colleagues) is less sensitive than MoCA for identifying mild deficits and the MMSE may be a better choice for patients with advanced disease who cannot complete the MoCA (should note length of time required for the patient to complete the MoCA).

- **Screening neurological examination**
- **Laboratory and neuroradiological evaluations**

### Causes of Dementia and Associated Characteristics

#### Mild Cognitive Impairment (MCI)

- **Definition:** MCI is a condition in which an individual has **mild but measurable changes in thinking abilities** that are noticeable to the person affected and to family members and friends, but the individual is still able to carry out everyday activities. Concern over the use of the term MCI (the similar term is available in DSM-5) in clinical practice arises because of the heterogeneity of progression and etiologies.

- **Demographics**
  - Estimated prevalence - 15-20% in persons older than 65 years; risk state for dementia
  - Population-based studies – while up to 30% of persons diagnosed with MCI return to “normal” in a year, 30% develop Alzheimer disease in 5 years
  - Subjective cognitive complaints in elderly patients - 7-8% progress to MCI or dementia every year

- **Diagnostic Categories**
  - **Amnestic MCI** (can include other than memory domain; i.e. attention, language, visuospatial skills).
  - **Non-amnestic MCI** (attention, language, visuospatial skills)

- **Diagnosis**
  - Poor performance on **delayed recall and executive function tests** - high risk for progression to Alzheimer’s disease (predictive value of associated depression?).
    - Montreal Cognitive Assessment (MoCA) – usually abnormal
    - Mini-Mental State Examination (MMSE) - usually normal
  - Patterns of brain MRI abnormalities in the amnestic group that identifies those who will later develop Alzheimer disease. (PET imaging of brain amyloid and Tau appear to distinguish between normal, MCI and Alzheimer’s disease.)
  - Systematic screening for dementia in asymptomatic elderly is not recommended

- **Treatment**
  - **AChEIs are currently not approved/shown to influence the underlying disease process or progression to dementia.** Control of other health risk factors is a more appropriate undertaking.
### Specific Causes of Dementia and Associated Characteristics

<table>
<thead>
<tr>
<th>Cause</th>
<th>Characteristics</th>
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| Alzheimer disease             | - Most common cause of dementia; accounts for an estimated 60 percent to 80 percent of cases. Autopsy studies show that about half of these cases involve solely Alzheimer’s pathology; many of the remaining cases have evidence of additional pathologic changes related to other dementias. This is called mixed pathology, and if recognized during life is called mixed dementia.  
- Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavioral changes and, ultimately, difficulty speaking, swallowing and walking.  
- Alzheimer disease is considered a slowly progressive brain disease that begins well before clinical symptoms emerge.  
- The hallmark pathologies of Alzheimer’s are the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (neurofibrillary tangles) inside neurons. These changes are eventually accompanied by the damage and death of neurons.  
- Vascular dementia occurs most commonly from blood vessel blockage or damage leading to infarcts (strokes) or bleeding in the brain. The location, number and size of the brain injuries determine whether dementia will result and how the individual’s thinking and physical functioning will be affected.  
- In the past, evidence of vascular dementia was used to exclude a diagnosis of Alzheimer’s (and vice versa). That practice is no longer considered consistent with the pathologic evidence, which shows that the brain changes of Alzheimer’s and vascular dementia commonly coexist. When there is clinical evidence of two or more causes of dementia, the individual is considered to have mixed dementia. |
| Vascular dementia             | - People with DBL have some of the symptoms common in Alzheimer but are more likely to have initial or early symptoms of sleep disturbances, well-formed visual hallucinations, and slowness, gait imbalance or other parkinsonian movement features. These features, as well as early visuospatial impairment, may occur in the absence of significant memory impairment.  
- Lewy bodies are abnormal aggregations (or clumps) of the protein alpha-synuclein in neurons. When they develop in a part of the brain called the cortex, dementia can result. Alpha-synuclein also aggregates in the brains of people with Parkinson’s disease (PD), in which it is accompanied by severe neuronal loss in a part of the brain called the substantia nigra.  
- While people with DBL and PD both have Lewy bodies, the onset of the disease is marked by motor impairment in PD and cognitive impairment in DBL.  
- The brain changes of DBL alone can cause dementia, but very commonly people with DBL have coexisting Alzheimer pathology. In people with both DBL and Alzheimer’s pathology, symptoms of both diseases may emerge and lead to some confusion in diagnosis. Vascular dementia can also coexist and contribute to the dementia. When evidence of more than one dementia is recognized during life, the individual is said to have mixed dementia. |
| Dementia with Lewy bodies (DLB) | - Characterized by the hallmark abnormalities of more than one cause of dementia — most commonly Alzheimer combined with vascular dementia, followed by Alzheimer’s with DBL, and Alzheimer’s with vascular dementia and DBL.  
- Vascular dementia with DBL is much less common.  
- Recent studies suggest that mixed dementia is more common than previously recognized, with about half of older people with dementia having pathologic evidence of more than one cause of dementia. Recent studies also show that the likelihood of having mixed dementia increases with age and is highest in the oldest-old (people age 85 or older). |
| Mixed dementia                | - Includes dementias such as behavioral-variant FTLD, primary progressive aphasia, Pick’s disease, corticobasal degeneration and progressive supranuclear palsy.  
- Typical early symptoms include marked changes in personality and behavior and/or difficulty with producing or comprehending language. Unlike Alzheimer, memory is typically spared in the early stages of disease. 40% are associated with an AD pattern of inheritance.  
- Nerve cells in the front (frontal lobe) and side regions (temporal lobes) of the brain are especially affected, and these regions become markedly atrophied (shrunken). In addition, the upper layers of the cortex typically become soft and spongy and have abnormal protein inclusions (usually tau protein or the transactive response DNA-binding protein, TDP-43).  
- The symptoms of FTLD may occur in those age 65 years and older, like Alzheimer’s, but most people with FTLD develop symptoms at a younger age. About 60 percent of people with FTLD are ages 45 to 60. FTLD accounts for about 10 percent of dementia cases. |
| Frontotemporal dementia       | - Problems with movement (slowness, rigidity, tremor and changes in gait) are common symptoms of PD.  
- In PD, alpha-synuclein aggregates appear in an area deep in the brain called the substantia nigra. The aggregates are thought to cause degeneration of the nerve cells that produce dopamine.  
- The incidence of PD is about one-tenth that of Alzheimer.  
- As PD progresses, it often results in dementia secondary to the accumulation of Lewy bodies in the cortex (like DLB) or the accumulation of beta-amyloid clumps and tau tangles (like Alzheimer). |
| Parkinson disease (PD)        | - This very rare and rapidly fatal disorder impairs memory and coordination and causes behavior changes.  
- Results from a misfolded protein (prion) that causes other proteins throughout the brain to misfold and malfunction.  
- May be hereditary (caused by a gene that runs in one’s family), sporadic (unknown cause) or caused by a known prion infection.  
- A specific form called variant Creutzfeld-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease. |
| Creutzfeldt-Jakob disease      | - Symptoms include difficulty walking, memory loss and inability to control urination.  
- Accounts for less than 5 percent of dementia cases.  
- Caused by impaired reabsorption of cerebrospinal fluid and the consequent buildup of fluid in the brain, increasing pressure in the brain.  
- People with a history of brain hemorrhage (particularly subarachnoid hemorrhage) and meningitis are at increased risk.  
- Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid. |
| Normal pressure hydrocephalus  | - Symptoms include difficulty walking, memory loss and inability to control urination.  
- Accounts for less than 5 percent of dementia cases.  
- Caused by impaired reabsorption of cerebrospinal fluid and the consequent buildup of fluid in the brain, increasing pressure in the brain.  
- People with a history of brain hemorrhage (particularly subarachnoid hemorrhage) and meningitis are at increased risk.  
- Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid. |
ALZHEIMER DISEASE

• Definition: Chronic neurodegenerative disorder and the most common cause of dementia; currently a definitive diagnosis is made by histopathologic examination of brain tissue. The neuropathologic “hallmarks” include amyloid-rich plaques, neurofibrillary tangles of phosphorylated tau protein, neuron degeneration and synaptic loss. (The pre-clinical/presymptomatic stage, undetectable by current clinical methods, may be identified by biomarkers, SPECT or PET imaging).

• Pathophysiology

“Amyloid cascade hypothesis” proposed as the underlying pathogenesis (now being questioned) of AD with accumulation and aggregation of a toxic and insoluble form of amyloid fibrils (and this protein misfolding can extend by intercellular spreading). This hypothesis is supported by mutations in three genes: presenilin 1 (PSEN1) – chromosome 14, presenilin 2 (PSEN2) – chromosome 1 and amyloid precursor protein (APP) – chromosome 21; all are associated with an autosomal dominant early-onset form of Alzheimer disease. The APOE ε4 allele is associated with increased risk of AD. All of these genetic disorders are involved in production or processing of β-amyloid. Resulting neurotransmitter changes:

  o Acetylcholine - an important neurotransmitter in areas of the brain that have role(s) in memory and loss of these neurons correlates with the severity of AD
    ▪ Rationale for cholinesterase inhibitors that increase acetylcholine levels
  o Presynaptic nicotinic receptors control the release of neurotransmitters important for memory and mood; in AD there is a selective loss of nicotinic receptor subtypes in the hippocampus and cortex.
    ▪ Drugs that act on those receptors exert a neuroprotective effect and reduce the burden of amyloid accumulation
  o Evidence of increased excitotoxicity from an increase in glutamatergic stimulation of N-methyl-D-aspartate (NMDA) receptors in AD; leads to high intracellular levels of calcium and cell death (NMDA receptors are a molecular device for controlling synaptic plasticity and memory function).
    ▪ Rationale for the use of a NMDA receptor antagonists

VASCULAR COGNITIVE IMPAIRMENT (VCI)

• Definition: (Older terms include multi-infarct dementia (MID), subcortical arteriosclerotic encephalopathy and Binswanger’s disease). Presently there are no combinations of features or criteria capable of diagnosing vascular dementia, with a high sensitivity, and in part because of the heterogeneous nature of cerebrovascular disease. However, it may be the second most frequent cause/contributor to all dementias (sole cause ~ 10%). As many as 30% of stroke survivors had dementia, six months after their stroke and their overall survival rates were worse.

• Diagnostic Categories
  o Clinical Criteria:
    ▪ The cognitive profile includes prominent psychomotor slowing and executive dysfunction with relatively preserved language and recognition memory all reflecting the subcortical sites of injury. (In cognitively impaired elderly patients, AD cannot be excluded and is the most common alternative diagnosis, but more likely to play a minor role in patients who are younger than 65. Deterioration in VCI may be gradual and progressive, not step-wise and further mimicking AD).
  o Vascular Dementia subtypes:
    ▪ Large vessel disease
    ▪ Small vessel vascular dementia
    ▪ Ischemic-hypoperfusion vascular dementia
    ▪ Hemorrhagic vascular dementia
Demographics: Similar risk factors as those for cerebrovascular and heart disease, but include advanced age and certain ethnic groups (Asians and African-Americans). In general, the role of genetic factors is not clear. White matter hyperintensities and lacunes on MRI/CT are independently associated with cognitive impairment in older persons. Similar to AD, higher educational level may be a “protective” factor.

DEMENTIA WITH LEWY BODIES
- **Definition:** Dementia with Lewy bodies (DLB or LBD) is the third or second most common form of degenerative dementia in old age and combines some of the features of AD and Parkinson’s disease. The clinical presentation is characterized by: **fluctuating cognitive impairment**, prominent attentional deficits, and **visuospatial dysfunction**, accompanied by **persistent complex visual hallucinations**, and **mild extrapyramidal features**.

  The identification of Lewy bodies and Lewy neurites, especially in brainstem nuclei, limbic and neocortical areas by immunohistochemical staining for alpha-synuclein helps to establish the diagnosis. Likelihood that the observed histopathology explains the LBD clinical syndrome is directly related to the severity of Lewy-body related pathology, and inversely related to the severity of concurrent AD-type pathology.

- **Treatment:**
  - AChEI’s - beneficial for both cognition and behavior (donepezil and memantine in moderate or severe stage?) - but may worsen autonomic system dysfunction
  - Melatonin or low dose clonazepam (0.5 to 2.0 mg) at bedtime - helpful with the REM sleep disorder
  - Sinemet™ in low doses with gradual titration - helps with motor function; may exacerbate psychosis
  - Quetiapine (Seroquel™) at low doses - may be the “drug of choice” for behavioral disturbances (be cognizant of the FDA black box warning) – **Risperidone and the typical antipsychotics should not be given in DLB**

FRONTOTEMPORAL DEMENTIA
- **Definition:** Frontotemporal Dementia, FTD (Pick’s disease or complex, Frontotemporal lobar degeneration) a diverse group of clinical and pathologic disorders characterized by profound changes in personality, social conduct and associated with circumscribed degeneration in the prefrontal and temporal lobes. Histological features include neuronal loss, microvacuolization and astrocytic gliosis, but one major difference among the subtypes is the presence or absence of tau histochemical staining on pathologic examination. In an individual case, the underlying histological changes cannot be inferred.

  No male/female difference in incidence, onset is between 45-65 years of age, duration of illness is 6-8 years. While representing perhaps 10% of degenerative dementias, it is the second most common cause of early onset dementia after early onset Alzheimer disease. (FDG-PET may identify anterior areas of cerebral hypometabolism and a pattern that can distinguish it from AD).

  **Family history is common (present in 40-50%):** mutation of the microtubule associated protein tau (**MAPT**), that regulates microtubule assembly, disassembly and transport of proteins and organelles, and results in deposition of a hyperphosphorylated tau protein. Progranulin (**GRN** or **PGRN**) gene mutations and **C90RF72**, both associated with deposition of transactive response DNA binding protein 43 (TDP-43), may both be as frequent a mutation as **MAPT**.
• Diagnostic Categories
  o **Behavioral variant of FTD (bvFTD - abnormality in the frontal and/or anterior temporal lobes)**
    ▪ Insidious onset and gradual progression (50% of FTD cases, avg. age of 58 years)
    ▪ Early decline in social and interpersonal conduct, regulation of personal conduct (Executive functions such as planning, judgment, problem solving, organization, attention, abstraction, and mental flexibility)
    ▪ Early emotional blunting
    ▪ Early loss of insight (difficulty in inferring what people think or feel) – less often encountered
  o **Treatment Options:**
    ▪ Compulsive or carbohydrate cravings – SSRI’s (citalopram or trazodone (100 mg tid))
    ▪ Obsessive/compulsive behavior – SSRI’s (citalopram or trazodone (100 mg tid))
    ▪ Aggressive/delusional behavior – SSRI’s (citalopram or trazodone (100 mg tid))
    ▪ Cognitive – No clear recommendations (acetylcholinesterase inhibitors may increase agitation)

  o **Primary progressive aphasias** are characterized by the insidious and progressive loss of language with relative sparing of other cognitive domains. Majority of remaining cases of FTLD. (Pathological studies demonstrate that 20-37% of these cases have AD pathology at autopsy!)
    • **Non-fluent variant primary progressive aphasia** *(abnormality in left inferior frontal gyrus and anterior insula)*
      ▪ Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia
    • **Semantic variant primary progressive aphasia** *(abnormality in left anterior temporal lobe)*
      ▪ Fluent, but empty spontaneous speech. Loss of word meaning, manifested by impaired naming and comprehension, semantic paraphasias

  o **Progressive Supranuclear Palsy (PSP)**
    ▪ Insidious onset and gradual progression
    ▪ Onset at age 40 years or older
    ▪ Vertical supranuclear palsy with downward gaze abnormalities, marked postural instability, rigidity and falls in the first year of symptom onset

  o **Corticobasal syndrome (Extrapyramidal, apractic, supranuclear palsy presentation)**
    ▪ Insidious onset and gradual progression
    ▪ Nonfluent spontaneous speech (agrammatism, phonemic paraphasias, anomia) with at least one of the following: asymmetric rigidity, apraxia, and **alien limb phenomenon** (limb seems to move without volitional control)
    ▪ **TREATMENT:** limited response to L-dopa, Clonazepam for myoclonus and dystonia

**RAPIDLY PROGRESSIVE DEMENTIAS**

<table>
<thead>
<tr>
<th>Potentially reversible conditions</th>
<th>Fatal, irreversible conditions</th>
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<tbody>
<tr>
<td>• Autoimmune/inflammatory encephalopathies</td>
<td>• Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td>• <strong>Toxic disturbances</strong>*</td>
<td>• FTL dementia, DLBD, Alzheimer disease may also present with a rapidly progressive dementia (&lt; 4 years from onset to death)</td>
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<td>• Metabolic disturbances</td>
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<td>• Depressive disorders</td>
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<td>• Vasculitic conditions affecting the brain</td>
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<td>• Brain structural lesions</td>
<td>• Paraneoplastic limbic encephalitis</td>
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<tr>
<td>• Subacute chronic meningitis or encephalitis</td>
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*May have significant long term morbidity (**Post-Operative Cognitive Dysfunction, POCD**)*
**Principles and Goals of treatment strategies for Alzheimer’s disease**

- Establishing an early and accurate clinical diagnosis of AD
- Early institution of acetylcholine esterase inhibitors and/or NMDA receptor-targeted drugs
- Treating medical comorbidities and dementia-related complications
  - Treat cardiovascular risk factors, adjust therapy in renal or hepatic disease, remove anticholinergics
  - Don’t discontinue therapy during illness or hospitalization, or if done, reinstitute as soon as possible
  - What is the role of therapy when patients have advanced to a loss of all cognitive/functional abilities?
- Ensuring that appropriate services are provided
- Addressing long-term well-being of caregivers
  - Counsel patients and caregivers about the realistic expectations of treatment
  - Most are women, over 50 years of age, spend from 40-100 hrs./week with the person who has AD
  - Ninety percent are affected emotionally (frustrated, drained) and 66% have significant depression
  - “Breaking point” for caregivers – the amount of time spent caring for the person, loss of identity, patient misidentifications, clinical fluctuations, and patient nocturnal deterioration

**Treatment:**

- **Behavioral symptoms of AD: Non-pharmacological intervention**
  - Behavioral modification (i.e., graded assistance, music during activities, walking or other forms of light exercise) may be the best first approach for behavioral and psychiatric symptoms in people with dementia.

- **Behavioral symptoms of AD: General tenets – pharmacologic**
  - Identify target symptoms and concentrate on addressing one at a time
  - Quantify adverse behaviors; (allow assessment of efficacy through measurement of partial outcomes)
  - “Remove” other possible precipitants of adverse behavior; medications (benzodiazepines, anticholinergics, etc.), environmental (intrapersonal - pain, constipation; interpersonal - spousal conflict, overstimulation, personal care activities) and physical (too hot, too cold, etc.)
  - You and the family need to be aware of **Black Box warnings (SSRIs also increase fall risk!)**
  - Sequential monotherapy, one drug at a time, low dose & gradually increase, consider treatment for 3-6 months and then gradual elimination if no longer needed
  - **Neuroleptic (Antipsychotic) Medications:**
    - **Typical neuroleptic medications:** Developed for schizophrenia, dose based on the potency of dopamine D2 receptor antagonism, the mechanism of action and reason they cause Parkinsonism and tardive dyskinesia. Haloperidol (Haldol™) is the most widely prescribed. All these drugs have a **black box warning:** not approved for dementia-related psychosis because of increased mortality risk.
    - **Atypical neuroleptic or antipsychotic medications:** Have a lower D2 receptor antagonism and act as 5-HT2A receptor antagonists. They had accounted for >80% of the neuroleptics prescribed for people with dementia. Risperidone (Risperdal™), olanzapine (Zyprexa™), and quetiapine (Seroquel™) were the most widely prescribed. All these drugs now have a **black box warning:** not approved for dementia-related psychosis because of increased mortality risk.

  - Treatment-unresponsive agitation and aggression are the most frequent reasons for the institutionalization of Alzheimer disease patients (as well as identification and treatment of physical and medical precipitants). The **CATIE-AD** (Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s disease) found that the drugs used were more effective than placebo, but adverse effects limited their overall effectiveness and their use “may be restricted to patients who have few or no side effects and for whom benefits may be discerned”
### Pharmacologic Treatment for Non-Cognitive Symptoms - some general “recommendations”

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Agent</th>
<th>“Usual” Daily Dose</th>
<th>Other comments</th>
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<tbody>
<tr>
<td><strong>Depression</strong></td>
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<tr>
<td></td>
<td><strong>Citalopram (Celexa™)</strong></td>
<td>5-10 mg (up to 20 mg)</td>
<td>Neutral effect on arousal, favorable drug interaction profiles</td>
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<tr>
<td></td>
<td><strong>Sertraline (Zoloft™)</strong></td>
<td>12.5-25 mg (up to 200 mg)</td>
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<td></td>
<td><strong>Fluoxetine (Prozac™)</strong></td>
<td>20 mg (up to 40 mg)</td>
<td>Generally arousing, can be a “favorable” side effect</td>
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<td><strong>Paroxetine (Paxil™)</strong></td>
<td>20 mg (up to 50 mg)</td>
<td>Somewhat more sedating</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td><strong>Trazodone (Desyrel™)</strong></td>
<td>50 mg (up to 300 mg)</td>
<td>When regular benzodiazepine use becomes necessary, consider these medications (Trazodone may be helpful with sundowning)</td>
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<td></td>
<td><strong>Buspirone (BuSpar™)</strong></td>
<td>5 mg bid (up to 45 mg)</td>
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<td></td>
<td><strong>Lorazepam (Ativan™)</strong></td>
<td>0.5 – 1.0 mg/per dose</td>
<td>Acute short-term anxiety, intermittent use</td>
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<td></td>
<td><strong>Clonazepam (Klonopin™)</strong></td>
<td>0.5 – 1.0 mg</td>
<td>“Maintenance” until long-term management is in place (taper slowly when discontinuing these agents)</td>
</tr>
<tr>
<td><strong>Psychosis</strong></td>
<td><strong>Quetiapine (Seroquel™)</strong></td>
<td>12.5 mg at bedtime or twice a day (up to 150 mg)</td>
<td>Associated sedation may help with nighttime hallucinations and poor sleep onset</td>
</tr>
<tr>
<td></td>
<td><strong>Haloperidol (Haldol™)</strong></td>
<td>0.5 mg/per dose</td>
<td>For severe acute episodes; <strong>Not for DLB</strong></td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td><strong>Citalopram (Celexa™)</strong></td>
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</tr>
<tr>
<td>&amp; Aggression</td>
<td><strong>Trazodone (Desyrel™)</strong></td>
<td>50 mg (up to 300 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Quetiapine (Seroquel™)</strong></td>
<td>12.5 mg at bedtime or twice a day (up to 150 mg)</td>
<td>Associated sedation may help with nighttime hallucinations and poor sleep onset</td>
</tr>
<tr>
<td></td>
<td><strong>Mirtazapine (Remeron™)</strong></td>
<td>15 - 30 mg at bedtime</td>
<td>Sedation, headache, and hypotension are side effects</td>
</tr>
<tr>
<td></td>
<td><strong>Risperidone (Risperdal™)</strong></td>
<td>1 mg at bedtime</td>
<td><strong>NOT for DLB dementia</strong></td>
</tr>
</tbody>
</table>

* Anxiety is a frequent concomitant of depression so, treatment should first proceed as for depression

* In April 2005, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

* FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

⇒ Antipsychotics are not indicated for the treatment of dementia-related psychosis.
### Pharmacologic Treatment Guidelines for Alzheimer’s disease – cognitive*

<table>
<thead>
<tr>
<th>Stage</th>
<th>First line Therapy</th>
<th>Treatment failure or loss of effectiveness</th>
<th>Treatment failure or loss of effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild to Moderate</strong></td>
<td><strong>Donepezil (Aricept™)</strong></td>
<td>Switch to <strong>Rivastigmine</strong> or <strong>Galantamine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initiate with 5 mg at bedtime and at 4 weeks, increase to 10 mg at bedtime</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum therapeutic dose is 5 mg at bedtime</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum therapeutic dose is 10 mg at bedtime</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Galantamine (Razadyne™)</strong></td>
<td>Switch to <strong>Rivastigmine</strong> or <strong>Donepezil</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initiate with 4 mg bid (with meals) and at 4 week intervals, increase each dose by 4 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum therapeutic dose is 8 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum therapeutic dose is 12 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rivastigmine (Exelon™)</strong></td>
<td>Switch to <strong>Memantine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Exelon® Patch: 4.6 mg/24 hours, after four weeks 9.5 mg/24 hours (13.3 mg/24 hour, suggests a benefit over 9.5 mg?)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initiate with 1.5 mg bid (at end of meal) and at 4 week intervals, increase each dose by 1.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum therapeutic dose is 3 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum therapeutic dose is 6 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Donepezil (Aricept™) – 23 mg dose??</strong></td>
<td>Switch to <strong>Rivastigmine</strong> or <strong>Galantamine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(plus Memantine)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Galantamine (Razadyne™)</strong></td>
<td>Switch to <strong>Rivastigmine</strong> or <strong>Donepezil</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(plus Memantine?)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rivastigmine (Exelon™)</strong></td>
<td>Switch to <strong>Galantamine</strong> or <strong>Donepezil</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(plus Memantine?)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td><strong>Memantine (Namenda™)</strong></td>
<td>Add? <strong>Donepezil, Rivastigmine or Galantamine</strong></td>
<td></td>
</tr>
<tr>
<td>(Previously untreated)</td>
<td>Initiate with 5 mg at bedtime, at 1 week intervals, increase by 5 mg, bid schedule and up to 10mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Memantine ER</strong> <em>(7mg for 1 week, increase 7mg/week and up to 28 mg/day)</em></td>
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<td></td>
</tr>
<tr>
<td></td>
<td><strong>Memantine (Namenda™)</strong></td>
<td>Add? <strong>Rivastigmine or Galantamine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Donepezil (Aricept™) – 23 mg dose??</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(plus Memantine)</em></td>
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<td></td>
</tr>
</tbody>
</table>

* Use caution in cases where EKG abnormalities are present, asthma or COPD, PUD or NSAID use

To determine clinical effectiveness a treatment trial of at least six months is required. Switching guidelines for Rivastigmine and Galantamine can be safely accomplished without a washout period if no safety/tolerability issues were evident with the initial agent, otherwise a washout period of 7-14 days.

For patients who have discontinued a cholinesterase inhibitor for more than one week, as a precaution it is recommended that they be re-titrated up to their therapeutic dose (treatment gaps of up to six weeks don’t compromise outcome).