Approach to Dementia

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Overview

- Diagnostic Criteria for Dementia
- Diagnostic Criteria for Alzheimer’s Disease
- Differential diagnosis
- Pathophysiology of the Alzheimer’s Disease
- Case presentations
Definition

- Development of multiple cognitive deficits manifested by
  - Memory impairment
  - One of the following cognitive disturbances
    - Aphasia
    - Apraxia
    - Agnosia
    - Disturbance in executive function

- The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

- The deficits do not occur exclusively during the course of a delirium

DSM-IV-TR criteria for dementia, 1994

Core Clinical Criteria
Dementia

- Cognitive impairment is detected and diagnosed through a combination of
  - (1) history-taking from the patient and a knowledgeable informant and
  - (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing.

- Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

Core Clinical Criteria
Dementia

- The cognitive or behavioral impairment involves a minimum of two of the following domains:
- Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.


Core Clinical Criteria
Dementia

- Impaired reasoning and handling of complex tasks, poor judgement—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
- Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body.

Core Clinical Criteria

Dementia

- Impaired language functions (speaking, reading, writing)-symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling and writing errors.
- Changes in personality, behavior, or comportment-symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiate, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive, or obsessive behaviors, socially unacceptable behaviors.


Core Clinical Criteria

Dementia

- Dementia is diagnosed when there are cognitive or behavioral symptoms that:
  - Interfere with the ability to function at work or at usual activities and
  - Represent a decline from previous levels of functioning and performing and
  - Are not explained by delirium or major psychiatric disorder.

### Core Clinical Criteria

- **Probable AD dementia**
- **Possible AD dementia**
- **Probable or possible AD dementia with evidence of the AD pathopsysiological process**

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### Core Clinical Criteria

- **Probable AD is diagnosed when:**
  - Dementia
  - Insidious onset
  - Clear –cut history of worsening of cognition by report or observation and
  - The initial and most prominent cognitive deficits are evident by history and examination in one of the following:
    - Amnestic presentations
    - Non Amnestic presentations (Language, Visuospatial presentation, executive dysfunction)

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The 3 Ds in the differential diagnosis

- Dementia
- Delirium
  - Acute confusional state
  - Attention, concentration deficits,
  - fluctuations,
  - psychomotor and or autonomic
    overactivity,
  - fragmented speech, hallucinations
- Depression

VITAMINS

Mnemonic for Differential Categories of RPDs

- Vascular
- Infectious
- Toxic-Metabolic
- Autoimmune
- Metastases
- Iatrogenic
- Neoplastic/Neurodegenerative
- Systemic

M Geschwind AAN syllabus 07
### Differential Diagnosis

- Vascular diseases
  - Vascular dementia
  - Cerebral amyloid angiopathy
  - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
  - Vasculitis

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80 yo WM with AF episodic confusion and progressive cognitive deficits
### Differential Diagnosis

#### Infections

- HIV
- Neurosyphilis
- Progressive multifocal leucoencephalopathy
- Subacute sclerosing panencephalitis
- Acquired CJD
- Whipple disease
- Encephalitis (bacterial, viral, fungal, rickettsial)
- Infection in older adults (urinary tract infection, pneumonia etc)

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- 39 yo WM with HIV/AIDS, incidental diagnosis three years ago, now with frontal dysexecutive dysfunction and hypersexuality.
- MMSE 22/30
# Differential Diagnosis

## Toxic Metabolic

<table>
<thead>
<tr>
<th>Electrolyte abnormality (na, K, Ca, Mg, P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Iatrogenic medication</td>
</tr>
<tr>
<td>Bismuth encephalopathy</td>
</tr>
<tr>
<td>Wernicke’s syndrome</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Organic solvent ingestion</td>
</tr>
<tr>
<td>Extrapontine myelinolysis</td>
</tr>
<tr>
<td>Heavy metals intoxication</td>
</tr>
<tr>
<td>Wilson Disease</td>
</tr>
<tr>
<td>Vitamin Deficiencies (b12, Niacin)</td>
</tr>
<tr>
<td>Hyperparathyroidism or other endocrine dysfunction</td>
</tr>
<tr>
<td>Uremic encephalopathy</td>
</tr>
<tr>
<td>Acquired Hepatocerebral degeneration</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
</tr>
<tr>
<td>Post brain radiation</td>
</tr>
</tbody>
</table>

## Dementia syndromes associated with alcohol

<table>
<thead>
<tr>
<th>Amnestic syndrome (Korsakoff’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnestic disorder predominates-confabulations</td>
</tr>
<tr>
<td>Generalized dementia associated with alcoholism</td>
</tr>
<tr>
<td>Visuospatial impairment</td>
</tr>
<tr>
<td>Alcohol related delirium-Wernicke’s encephalopathy</td>
</tr>
<tr>
<td>Confusion, eyes abnormalities and ataxia</td>
</tr>
</tbody>
</table>
### Differential Diagnosis

#### Autoimmune

- Anti-NMDA paraneoplastic
- Acute demyelinating encephalomyelitis
- CNS vasculitis/cerebritis
- Hashimoto encephalopathy
- Sprue
- Sarcoid
- Behcet
- Anti-glutamic acid decarboxylase, 65 isoform
- Paraneoplastic limbic encephalopathy (anti-Hu, CV2, Ma/ta, VGKC, NMDA, neuropil)

#### Metastases

- Infiltrating tumors
- Lymphoma
- Paraneoplastic encephalopathy
### Differential Diagnosis

**Iatrogenic**

- Hospitalization of older adults/sundowning
- Medications (e.g. methotrexate)

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### Differential Diagnosis

- Neurodegenerative dementias
  - Alzheimer’s disease
  - Lewy Body Dementia
  - Frontotemporal dementia
  - Huntington’s disease
  - Progressive supranuclear palsy
  - Corticobasal ganglionic degeneration
  - Multiple system atrophy
  - Wilson’s disease
  - Hemochromatosis/hemosidirosis
  - Neuronal ceroid lipofuscinosis
### Differential Diagnosis

<table>
<thead>
<tr>
<th>A-Synucleinopathies</th>
<th>Taupathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA</td>
<td>AD</td>
</tr>
<tr>
<td>PDD</td>
<td>PSP</td>
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<tr>
<td>DLB</td>
<td>CBD</td>
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<tr>
<td></td>
<td>FTLD</td>
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<table>
<thead>
<tr>
<th>Amyloidopathies</th>
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<tbody>
<tr>
<td>AD</td>
</tr>
<tr>
<td>DLB</td>
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<tr>
<td>PDD</td>
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</tbody>
</table>

### Differential Diagnosis

*Neurodegenerative dementias*

- **Parkinson disease with dementia**
  - Parkinsonism initially, later onset of dementia
- **Dementia with Lewy bodies**
  - Recurrent visual hallucinations, fluctuating cognition, variable parkinsonian signs
- **Progressive Supranuclear Palsy**
  - Balance and bulbar dysfunction, downgaze palsy
- **Corticobasal Syndrome**
  - Asymmetric limb signs (apraxia, myoclonus)
- **MSA**
  - Cerebellar type: Brainstem/cerebellar atrophy, ocular dysmotility
  - Parkinsonian type: Motor parkinsonism, dysautonomia
Historical Data…

On a Peculiar Disease of the Cerebral Cortex;
A. Alzheimer (1907)

A woman, 51 years old, showed jealousy towards her husband…
Soon, rapidly increasing loss of memory could be noticed… At times she would think that someone wanted to kill her …
She was totally disoriented to time and place …
Periodically, she was totally delirious,…and seemed to have auditory hallucinations….
When reading, she went from one line into another, reading the letters or reading with senseless emphasis …
When talking she frequently used perplexing phrases and some paraphasic expressions (milk-pourer instead of cup) …
She seemed no longer to understand the use of some objects …
The generalized dementia progressed … After 4 1/2 years of the disease, death occurred.

80 yo WM with three years history of slowly progressive cognitive deficits.
MMSE 21/30
B12, TSH nl
### Differential Diagnosis

**Prion Diseases**
- Creutzfeldt-Jacob disease
- Gerstmann-Straussler-Scheinker syndrome
- Kuru
- Fatal familial insomnia

### Structural - Systemic

- **Structural abnormalities**
  - Chronic subdural hematomas
  - Normal pressure hydrocephalus

- **Systemic**
  - Delirium
  - Hypertensive Ecephalopathy
  - Mitochondrial
64 yo wf with 2 years h/o gait apraxia, urinary incontinence and dementia

Practice Recommendations

- Structural neuroimaging (Guideline).
- Depression (Guideline).
- B12 deficiency (Guideline).
- Hypothyroidism (Guideline).

Knopman et al. Neurology Volume 56 • Number 9 • May 8, 2001
## Current Prevention

- Screening of patients elderly 65 years old by health care providers.
- Standardized questionnaires assessing cognition, function, mood, behaviors
- Early diagnosis and treatment
  - Clinical and financial benefit
  - Alleviate patient and caregiver burden
  - Reduce hospitalization time
  - Delay admission to NH

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## The evaluation of dementia

Detailed history from patient and collateral source
- Onset and duration of cognitive symptoms
- Areas of cognitive impairment
- Degree of functional impairment in ADLs and IADLs
- Driving
- Mood, psychosis, and behavioral symptoms
- Sleep disturbance
- Gait instability, or recurrent falls
- History of seizures, staring spells, or episodic confusion
- History of headaches
- Past medical history: vascular risk factors, strokes or TIA, TBI, chemotherapy, radiation, malignancy, cardiac disease
- Medications
- Family history especially for early onset cases (<65 yrs)
The evaluation of dementia

Detailed physical and neurological examination
- cortical deficits: apraxia, astereognosis, agraphesthesia
- language: naming, repetition, comprehension, and fluency
- signs of old stroke
- frontal release signs and primitive reflexes
- parkinsonism and gait abnormalities, gait apraxia
- dystonia, myoclonus, alien-limb
- signs of other systemic or medical illness (e.g. liver or renal disease)

Bedside cognitive testing to assess the degree and pattern of cognitive impairment
- Mini-Mental State Examination (MMSE)
- Self-Administered Gerocognitive Examination (SAGE)
- Montreal Cognitive Assessment (MoCA)
- Clock Drawing Test
- Blessed Dementia Scale

Screening for depression
Consider the need for more detailed neuropsychometric testing

Clock-drawing
Laboratory testing:

- **Routine testing for all patients:**
  - Complete blood cell count
  - Serum electrolytes
  - Glucose
  - BUN/creatinine
  - Vitamin B12 levels (also homocysteine and methylmalonic acid)
  - Thyroid function tests (TSH, T3, and T4)
  - Liver function test

- **Other tests only in high risk patients or when particular diagnoses are suspected:**
  - HIV, syphilis screening, Whipple's PCR, autoimmune/paraneoplastic panel, anti-thyroid antibodies, heavy metal screen, serum thiamine levels, ENA, ANA, RF, cryoglobulins, ANCA's, serum/urine protein electrophoresis/immunofixation

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Structural Brain Imaging

- Head computed tomography (CT) scan
- Brain magnetic resonance imaging (MRI)
  - Global or focal atrophy
  - Hippocampal and medial temporal atrophy in AD
  - Anterior temporal and frontal atrophy in frontotemporal dementia
  - Ischemic strokes, small vessel disease, microhemorrhages, subdural hematomas
  - Tumors (consider use of contrast)
  - Demyelinating disease (consider use of contrast)
  - Assess for communicating hydrocephalus
Brain MRI

Positron Emission Tomography (FDG-PET)
### CSF Analysis

- In atypical cases such as rapidly progressive dementias or when infection or malignancy are diagnostic considerations
- Cell count, protein, glucose, oligoclonal bands, and IgG index
- Viral, bacterial, mycobacterial, HIV, Whipple’s disease, VDRL, fungal infections
- Paraneoplastic/autoimmune panel, ACE
- Cytology and flow cytometry
- Testing for prion disorders (Creutzfeldt-Jakob disease)
- CSF tau and Aβ42

### EEG

- to rule out seizures if episodic symptoms, history of seizures, or staring spells

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### Treatment of Dementia
Overview:

- An accurate diagnosis is the first step in proper management
- Treat reversible causes of cognitive impairment
- Specific treatments for certain types of dementia
- For most neurodegenerative causes such as Alzheimer's disease, symptomatic treatments for cognitive impairment include:
  1. Cholinesterase inhibitors
  2. NMDA glutamate receptor agonist/antagonists
- There are no disease-modifying treatments
- Pharmacological treatment of behavioral symptoms
- Non-pharmacological treatment
- Counseling and education

Symptomatic dementia therapies

- Low acetylcholine levels
- Glutamate toxicity

- Cholinesterase - inhibitors
  - Increase acetylcholine levels at synapses
  - Improved cognition, behavior, and function

- NMDA agonist/antagonist
  - Block glutamate receptors

Low acetylcholine levels
Glutamate toxicity
Cholinesterase - inhibitors
NMDA agonist/antagonist
Increase acetylcholine levels at synapses
Block glutamate receptors
Improved cognition, behavior, and function
Neurochemical basis of AD symptoms

A. Cholinergic hypothesis:
- reduced acetylcholine (Ach) levels in hippocampus and neocortex
- loss of cholinergic neurons in the basal forebrain (e.g. nucleus basalis of Meynert)
- deficiency of the choline acetyl-transferase enzyme
- impaired uptake of choline
- impaired release of Ach
- degree of cholinergic deficit parallels the degree of cognitive and behavioral impairment

B. Glutamate toxicity: excess glutamate and Ca\(^{2+}\)-mediated excitotoxicity in AD

Symptomatic treatments for AD

<table>
<thead>
<tr>
<th>Pharmacological agent</th>
<th>Mechanism of action</th>
<th>Starting dose</th>
<th>Titration Schedule</th>
<th>Maximum dose</th>
<th>Indications for use</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (oral and ODT)</td>
<td>AChEI</td>
<td>5 mg po daily</td>
<td>Increase by 5 mg every 4 weeks</td>
<td>23 mg/day</td>
<td>All stages of dementia</td>
<td>Hepatic CYP2D6 and CYP3A4</td>
</tr>
<tr>
<td>Galantamine (oral regular and extended release forms)</td>
<td>AChEI and nicotinic receptor modulator</td>
<td>4 mg po twice a day (of ER 8 mg)</td>
<td>Increase by 4-8 mg/day every 4 weeks</td>
<td>12 mg po twice a day (or ER 24 mg)</td>
<td>Mild to moderate dementia</td>
<td>Hepatic CYP2D6 and CYP3A4</td>
</tr>
<tr>
<td>Rivastigmine (oral or transdermal patch)</td>
<td>AChEI and butyrylcholinesterase inhibitors</td>
<td>1.5 mg po twice a day</td>
<td>Increase by 1.5 mg po twice a day every 4 weeks</td>
<td>6 mg po twice a day</td>
<td>Mild to moderate dementia</td>
<td>Nonhepatic, renal clearance</td>
</tr>
<tr>
<td>Memantine (oral regular and extended release)</td>
<td>NMDA agonist/antagonist (partial agonist)</td>
<td>5 mg once a day (7 mg for XR)</td>
<td>Increase by 5 mg every week</td>
<td>10 mg po twice a day (28 mg for XR)</td>
<td>Moderate to severe dementia</td>
<td>Predominantly renal clearance</td>
</tr>
</tbody>
</table>
**Cholinesterase-inhibitors**

- Clinical trials and systematic reviews suggest a modest but significant benefit of all CHEI on cognitive, behavioral and functional measures in mild to moderate AD
  - Improvement in cognitive function (2.7 points on ADAS over 3-6 months)
  - Improvement in certain behavioral measures
  - Reduced functional decline with improved activities of daily living
  - Delay in nursing home placement

- Benefits of starting CHEI early in the disease course with no interruptions; benefits may extend up to 3-5 years

- If one CHEI is not tolerated, switching to another CHEI may be helpful

- Some CHEI have modest benefits in patients with severe AD dementia

- CHEI are also commonly used in the treatment of dementia with Lewy bodies, Parkinson disease dementia, and vascular dementia

**Donepezil**

- A multicenter, double-blinded study examined the efficacy and safety of donepezil in mild to moderate AD

  - This study randomized patients to placebo (n = 162), 5 mg/d donepezil (n = 154), or 10 mg/d donepezil (n = 157) for 24 weeks followed by a 6-week placebo washout period

  - Cognitive function, as measured by the ADAS-cog, was significantly improved in the 5- and 10-mg/d donepezil groups compared to placebo at weeks 12, 18, and 24

  - MMSE and CDR-SB also improved with treatment

  - Cholinergic side effects were transient and generally mild in severity

**Rivastigmine**

- A randomized clinical trial evaluated the safety and efficacy of rivastigmine in 699 patients with mild to moderate Alzheimer’s disease.
- Randomized to placebo (n=235), lower dose (1-4 mg/day) rivastigmine (n=233), or higher dose (6-12 mg/day) rivastigmine (n=231) for 26 weeks.
- Higher dose rivastigmine was associated with improvement in cognitive measures (ADAS-cog), global assessment of change (CIBIC-plus), and activities of daily living.
- GI side effects were self-limited, and of mild to moderate intensity.

Corey-Bloom et al. Int J Ger Psychopharmacol 1998; 155–65

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**Galantamine**

- A multicenter placebo-controlled double-blinded trial of galantamine over 5 months examined safety and efficacy of 8, 16, and 24 mg/day compared to placebo (n=978).
- The 16 and 24 mg/day doses were associated with improvement in cognitive measures (ADAS-cog), behavioral symptoms (NPI), and activities of daily living compared to placebo at the 5 month timepoint.
- Galantamine was well-tolerated with low incidence of side effects; mostly mild and related to GI symptoms.

**Memantine**

- N-methyl-D-aspartate (NMDA) receptor agonist/antagonist
- Possible neuroprotective effects
- Memantine has modest effects on cognition, behavior, and function in moderate to severe AD
- A 28-week randomized clinical trial of 252 patients with MMSE 3-14 showed that memantine (20 mg) was associated with reduced clinical deterioration (CIBIC-plus and the ADCS-ADL) compared to placebo and was well tolerated
- Memantine is useful as monotherapy or in combination with CHEI in moderate to severe dementia
- No evidence to support its use in mild dementia
- Memantine is also used in the treatment of vascular dementia


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**Combination of CHEI and memantine**

- In a 24-week trial (1), treatment with memantine plus donepezil resulted in significantly better outcomes than placebo plus donepezil on cognition, behavior, ADLs, and global outcomes in patients with moderate to severe dementia
- Another 24-week trial (2) compared memantine and placebo in patients with mild to moderate AD who were on a stable dose of CHEI (either donepezil, rivastigmine or galantamine) and showed no difference in outcomes between the groups
- Memantine is often used in combination with CHEI in moderate to severe dementia
- A combination capsule of donepezil and memantine in two different strengths is available

Fifth edition of APA’s Diagnostic and Statistical Manual of Mental Disorders

- Dementia is replaced by “major neurocognitive disorder”.
- Mild cognitive impairment is replaced by mild Neurocognitive Disorder.
- For purposes of this presentation will continue to use the terms Mild cognitive impairment and dementia because DSM-IV diagnoses were used in all the studies reviewed for this seminar.

American Psychiatric Association 2013

Behavioral symptoms

- Behavioral and neuropsychiatric symptoms are very common in Alzheimer’s Disease and other Dementias.
- They are distressing for patients with Dementia and caregivers.
- They can lead to increased mortality, excessive cognitive and function disability.
- Early institutionalization and caregiver burn out.
The Neuropsychiatric inventory as a checklist for behavioral issues

- Delusions
- Hallucinations
- Agitation/Aggression
- Depression
- Anxiety
- Elation
- Apathy
- Disinhibition

- Irritability
- Aberrant motor behaviors
- Sleep disturbances
- Eating disturbances


Management of behavioral disturbances in dementia

- Signs and symptoms in Dementias rarely fit into usual diagnostic classifications or meet full criteria for a formal major psychiatric disorder.
- There are currently no treatments approved by the US Food and Drug Administration.
- Both pharmacological and non pharmacological interventions should be included.
### Management of behavioral disturbances in dementia

- Non pharmacological interventions first line approach for treatment of agitation.
- Non pharmacological interventions can be difficult for patients with severe symptoms.
- Pharmacological interventions are often required for severe symptoms per guidelines but might be helpful even for several behavioral symptoms.

<table>
<thead>
<tr>
<th>Management of behavioral disturbances in dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ Match target symptoms to a medication with desired pharmacological effect.</td>
</tr>
</tbody>
</table>
| ✦ Avoid traditional neuroleptics:  
  Haloperidol- Cochrane Review 2002 |
| ✦ Start with a low dose and increase the dose slowly. |
| ✦ Expect improvement. |
| ✦ Once target symptoms have gone, slowly taper down to lowest effective dose or off. |
### Treatment options

<table>
<thead>
<tr>
<th>Symptom cluster</th>
<th>Common initial Med Choice</th>
<th>Possible Med Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis-Behavior</td>
<td>Atypical antipsychotic</td>
<td>SSRI, Trazodone, Valproate</td>
</tr>
<tr>
<td>Aggressive</td>
<td>Atypical antipsychotic</td>
<td>Trazodone, Valproate, SSRI</td>
</tr>
<tr>
<td>Irritable, oppositional</td>
<td>Trazodone</td>
<td>SSRI, Atypical antipsychotic</td>
</tr>
<tr>
<td>Mood, anxiety-labile, distress</td>
<td>SSRI</td>
<td>Valproate, Trazodone, Neudexta</td>
</tr>
<tr>
<td>Socially inappropriate, wandering, intrusive</td>
<td>Behavioral interventions</td>
<td>Valproate</td>
</tr>
</tbody>
</table>

### Management of psychosis and agitation

◆ The use of antipsychotic medications is recommended with moderate clinical evidence.

◆ Potential underlying causes should be addressed first, including environmental measures, reassurance and redirection.
Psychosocial interventions

Psychosocial interventions improve or maintain cognition, function, adaptive behavior, and quality of life.
Any specific psychosocial intervention is not more effective than another.
Support programs for caregivers and patients with dementia significantly decreased the odds of institutionalization and improved caregiver well-being.

APA guideline watch

FDA approved medications for Alzheimer’s disease dementia

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name</th>
<th>Approved For</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. donepezil</td>
<td>Aricept</td>
<td>All stages</td>
<td>1996</td>
</tr>
<tr>
<td>2. galantamine</td>
<td>Razadyne</td>
<td>Mild to moderate</td>
<td>2001</td>
</tr>
<tr>
<td>3. memantine</td>
<td>Namenda</td>
<td>Moderate to severe</td>
<td>2003</td>
</tr>
<tr>
<td>4. rivastigmine</td>
<td>Exelon</td>
<td>All stages</td>
<td>2000</td>
</tr>
<tr>
<td>5. donepezil and memantine</td>
<td>Namzaric</td>
<td>Moderate to severe</td>
<td>2014</td>
</tr>
</tbody>
</table>

*All other medications discussed in this talk are off-label use in dementia