Dementia: Opportunities & Challenges

Rajesh R. Tampi, MD, MS, DFAPA
Professor of Psychiatry
Case Western Reserve University School of Medicine
Vice Chairman for Education
Residency Program Director
Chief of Geriatric Psychiatry
MetroHealth, Cleveland, Ohio
Associate Clinical Professor of Psychiatry
Yale University School of Medicine
Disclosures

1. I will be discussing off-label use of cholinesterase inhibitors / NMDA antagonists in the treatment of some non-Alzheimer’s dementias.

2. I will be discussing future targets in treatment of neurocognitive disorders not yet FDA approved. *I do not endorse nor am I affiliated with the pharmaceutical companies testing these medications.*

3. I receive royalties for two books that I have published with Lippincotts Williams and Wilkins and one book with Nova Science, Inc. I also receive honoraria from Oakstone LLC, for being on their Editorial Board for Clinical Reviews in Psychiatry and for directing their Psychiatry Board Review Course.
Mild Cognitive Impairment (MCI)

The term is used to define cognitive changes beyond what is considered normal for age, but not severe enough to meet the diagnostic criteria for dementia or Alzheimer’s disease.

Prevalence

- 10% to 25% depending on the inclusion criteria, the nature of the population under study and the length of the follow-up period.

Increased prevalence

- Older age
- Men
- Never married
- APOE epsilon3epsilon4 or epsilon4epsilon4 genotype

Reduced prevalence

- Increasing number of years of education.
Subtypes of MCI:

- **Amnestic**: If the memory impairment is greater than what is expected for age and education.
- **Non-amnestic MCI**: If the person’s memory is relatively spared but there are impairments in non-memory cognitive domains such as language, visuospatial skills or executive functioning.

Sub-classification:

- **Amnestic MCI**
  - **Single domain**: If there is impairment of only memory domain.
  - **Multiple domain**: There are impairments in memory and other cognitive domains including language, visuospatial skills and executive functioning.

- **Non-amnestic MCI**
  - **Single domain**: Have impairment in a single non-memory domain
  - **Multiple domain**: Patients have impairments in multiple non-memory domains.

Amnestic subtype of MCI versus non-amnestic subtype; prevalence rate of 11.1% to 4.9%.

Most common cause for MCI was neurodegenerative conditions especially for amnestic subtype of MCI.
Neuropathology

- Intermediate neuropathologic changes between normal aging and very early Alzheimer’s disease (AD).

- Patients with amnestic MCI had pathologic findings involving medial temporal lobe structures and agyrophilic grain disease, hippocampal sclerosis, and vascular lesions.

Consequences

- Amnestic MCI patients progress to Alzheimer’s disease: 10% to 15% per year.

- These rates are greater than the population incidence figures for Alzheimer’s disease at 1% to 2% per year.

Risk factors for progression

1. **Degree of cognitive impairment**
   - Patients with more severe memory impairment amnestic MCI-multiple domain subtype

2. **Apolipoprotein E-ε4 (ApoE4) carrier status**
   - Apolipoprotein E-ε4 (ApoE4) carrier status

3. **Brain changes**
   - Hippocampal atrophy
   - Greater ventricular annual percent volume change
   - Greater whole brain annual percent volume change

4. **Cerebrospinal fluid (CSF) changes**
   - Combination of CSF T-tau and Abeta42 at baseline

At the present time, single and multimarker models have similar short-term predictive capability for the conversion of amnestic MCI subjects to AD.
## Treatments

<table>
<thead>
<tr>
<th>Nutritional</th>
<th>• Lower consumption of fatty food, saturated fatty acids, and cholesterol is associated with reduced cognitive decline in the elderly.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Stimulation</td>
<td>• Intellectually stimulating activities and cognitive intervention programs was associated with decreased risk of AD and decreased cognitive decline.</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>• A 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.</td>
</tr>
</tbody>
</table>
| Pharmacological Treatments | **1. Cholinesterase Inhibitors**  
  *Systematic review, Raschetti et al*  
  Relative risk (RR): 0.85  
  Rate of discontinuation: 24% vs. 13%  
  *Meta-analysis, Diniz et al*  
  Efficacy, RR: 0.75, P <0.001.  
  Side-effects, RR: 1.36, P< 0.001  
  **2. Anti-inflammatory drugs**  
  *Thal et al, Refecoxib vs. placebo*  
  Annual rate : 6.4% vs. 4.5%  
  Hazard ratio (HR):1.46, P=0.011  
  Adverse effects: 8.0% vs. 5.6%  
  **3. Antioxidants**  
  *Petersen et al, Vitamin E, Donepezil, Placebo*  
  HR: 1.02, 95% CI, P=0.91 or the donepezil group HR: 0.80, P=0.42 |
Dementias

DSM-IV-TR Diagnostic Criteria for Dementia

• Multiple cognitive deficits, including *impairment in memory*, and one or more of the following:
  - Aphasia
  - Apraxia
  - Agnosia
  - Executive dysfunction

• Impairment is severe enough to cause disturbance in functioning.

• Deficits do not occur exclusively during delirium.

• Not better accounted for by another Axis I diagnosis.
# DSM-5 Criteria

## Mild Neurocognitive Disorder
- Evidence of modest cognitive decline from previous level of performance in one or more cognitive domains
  - Subjective and objective concerns
  - Modest impairment in cognitive performance on standardized assessments
  - Do not interfere with capacity for independence in everyday activities
  - Not due to delirium or another mental disorder
- Due to AD, FTLD, Lewy Body disease, Vascular disease, TBI, Multiple etiologies….
- With or without behavioral disturbances

## Major Neurocognitive Disorder
- Evidence of significant cognitive decline from previous level of performance in one or more cognitive domains
  - Subjective and objective concerns
  - Substantial impairment in cognitive performance on standardized assessments
  - Cognitive deficits interfere with capacity for independence in everyday activities
  - Not due to delirium or another mental disorder
- Due to AD, FTLD, Lewy Body disease, Vascular disease, TBI, Multiple etiologies….
- With or without behavioral disturbances
- Mild, Moderate or Severe
### Cortical vs. Sub-Cortical

<table>
<thead>
<tr>
<th>Cortical</th>
<th>Subcortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alzheimer’s Disease</td>
<td>• Parkinson’s Disease Dementia</td>
</tr>
<tr>
<td>• Lewy Body Dementia</td>
<td>• Huntington’s Disease</td>
</tr>
<tr>
<td>• Frontotemporal Dementia</td>
<td>• Progressive Supranuclear Palsy</td>
</tr>
<tr>
<td>• Creutzfeldt-Jakob</td>
<td>• Normal Pressure Hydrocephalus</td>
</tr>
</tbody>
</table>

9
<table>
<thead>
<tr>
<th>Cortical</th>
<th>Subcortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnesia</td>
<td>Dysmnesia</td>
</tr>
<tr>
<td>• Loss of memory capacity</td>
<td>• Difficulty coordinating cognition → forgetfulness</td>
</tr>
<tr>
<td>Apraxia</td>
<td>Bradyphrenia and Bradykinesia</td>
</tr>
<tr>
<td>• Impaired ability to do learned motor tasks</td>
<td>• Slowed thinking/moving</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Dysexecutive function</td>
</tr>
<tr>
<td>• Language impairment</td>
<td>• Impaired decision-making</td>
</tr>
<tr>
<td>Agnosia</td>
<td>Depletion of thought</td>
</tr>
<tr>
<td>• Impaired recognition</td>
<td>• Reduced complexity of thought</td>
</tr>
</tbody>
</table>
Demographics

Prevalence of dementia
• 5-10% of population over 65
• 25-40% of population over 85

Etiologies of dementia are numerous
• Neurodegenerative disease the most common
  – AD (50-75%), FTD, DLB, Dementia due to PD/HD
• Vascular disease (15-30%)
• Trauma, infection, toxins
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dementia of the Alzheimer’s type (DAT)</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>Short term memory loss</td>
<td>Unfamiliarity with the environment with short term memory loss “confusion”</td>
<td>Subjective complaints of poor memory and concentration</td>
</tr>
<tr>
<td>Onset</td>
<td>Insidious</td>
<td>Sudden</td>
<td>Recent</td>
</tr>
<tr>
<td>Alertness</td>
<td>Normal except in late phases.</td>
<td>Fluctuating</td>
<td>Preserved</td>
</tr>
<tr>
<td>Duration</td>
<td>Months to years</td>
<td>Hours to weeks</td>
<td>Variable</td>
</tr>
<tr>
<td>Orientation</td>
<td>Disorientation occurs late in course</td>
<td>Disorientation with onset</td>
<td>Intact</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>May occur late in course</td>
<td>From onset</td>
<td>Could occur in depression with psychotic features</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>Progressive deterioration</td>
<td>Fluctuating with alertness</td>
<td>Initially intact with efforts to perform cognitive tasks. May deteriorate without treatment progression</td>
</tr>
<tr>
<td>Mood</td>
<td>Labile</td>
<td>Fluctuate</td>
<td>Usually sad</td>
</tr>
<tr>
<td>Sundowning</td>
<td>Present</td>
<td>Present</td>
<td>Absent, mood improve as day progress</td>
</tr>
<tr>
<td>Course</td>
<td>Irreversibility with progressive deterioration</td>
<td>Usually reversible with treatment</td>
<td>Completely reversible</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease

- Most common cause of dementia (50-75% cases).
- 5 million Americans afflicted; 9 million by 2030.
- Sixth leading cause of death in the United States

Presenting symptoms
- **Subtle difficulties in recent memory**
- Apathy, loss of interest in activities

Longitudinal course
- Progressive, continued cognitive decline
- Median survival from diagnosis (Larson et al 2004)
  - 4.2 years for men
  - 5.7 years for women
## Diagnostic Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preclinical AD</strong></td>
<td>No diagnostic criteria</td>
</tr>
<tr>
<td></td>
<td>Earliest stage of the disease</td>
</tr>
<tr>
<td><strong>MCI due to AD</strong></td>
<td>Mild changes in memory and thinking abilities, enough to be noticed and measured, but not impairment that compromises everyday activities.</td>
</tr>
<tr>
<td><strong>Dementia due to AD</strong></td>
<td>Cognitive and behavioral symptoms that impair an individual’s ability to function in daily life. Memory impairment may not be the central presenting feature, a decline in other aspects of cognition</td>
</tr>
</tbody>
</table>

### Biomarkers

**Biomarkers of beta-amyloid accumulation**
- Abnormal retention of beta-amyloid identifying tracer compounds on positron emission tomography (PET) imaging.
- Low levels of beta-amyloid 1-42 in cerebrospinal fluid (CSF).

**Biomarkers of neuronal degeneration or injury**
- Elevated levels of the protein tau (both total and phosphorylated tau) in CSF.
- Decreased fluorodeoxyglucose 18F (FDG) uptake on PET imaging in a specific pattern involving the brain’s temporo-parietal cortex.
- Atrophy on structural magnetic resonance imaging (MRI), again in a specific topographic pattern involving the brain’s medial, basal and lateral temporal lobes, and medial and lateral parietal cortices.
Neuropathology

- **Cortical atrophy**
  - Medial temporal lobe including hippocampus
  - Parietotemporal lobes

- **Neuritic plaques**: Extracellular, beta-amyloid core

- **Neurofibrillary tangles**: Intracellular inclusion bodies, hyperphosphorylated tau protein

- **Loss of cholinergic neurons** in critical areas of the brain (Nucleus basalis of Mynerts, hippocampus, frontal cortex, parietal cortex)
http://upr.org/post/alzheimers-disease-worldwide-collaboration-research
Work-up

A collateral informant is essential! Ask about…

- Cognitive changes
  - Acute, progressive, stepwise, fluctuating?
  - Associated with change in mood/behavior?

- Functional changes
  - B-ADL’s (D.E.A.T.H)
  - I-ADL’s (S.H.A.F.T.T)

- Past Psychiatric History
- Past Medical History
- Medications
- Family History
- Social History
  - Educational/occupational background
  - Recent change in social/living environment
  - Recent loss of spouse
Physical Examination
- Focal neurologic deficits
- Gait difficulties
- Pathologic reflexes
- Sensory impairments (vision, hearing)

Cognitive Testing
- Mental Status Examination
- Mini-Mental State Examination (MMSE)
- Clock Drawing
- Executive Interview (EXIT)
- Verbal fluency
- Abstraction: similarities/difference, proverb interpretation
- Calculations

Laboratory tests
- CBC with differential
- BUN/Cr, Electrolytes
- TSH
- Vit B12, Folate
- RPR or VDRL
- Liver Function Test
- UA/CS
- Urine toxicology screen
- HIV, ANA
- EKG
- Chest x-ray
- Lumbar puncture
Neuroimaging (CT/MRI)
- Acute onset/atypical presentation
- H/o trauma
- Focal neurologic findings, abnormal gait
- R/o NPH, neoplasm, subdural hematoma
- Evaluate for cerebrovascular disease, CVA

SPECT/PET Scan
- Useful to differentiate AD from FTD

EEG
- Delirium: generalized slow wave activity
- CJD: triphasic, periodic burst pattern
- Hepatic encephalopathy: triphasic waves

Neuropsychological testing
- Differentiating normal aging from early dementia and MCI
- Differentiating types of dementia (AD v. FTD v. VaD)
- Differentiating dementia from cognitive changes associated with depression
http://newscenter.berkeley.edu/2012/01/23/engaged-brain-amyloid-alzheimers
Early-Onset AD: Genetics

Familial: Autosomal Dominant

Amyloid Precursor Protein
- Chromosome 21
- Precursor molecule for generation of beta amyloid

Presenilin 1
- Chromosome 14

Presenilin 2
- Chromosome 1
Late-Onset AD

Apolipoprotein E

• Chromosome 19
• Susceptibility gene—does not guarantee AD
• 3 alleles: epsilon 2, 3, and 4
• Epsilon 4 allele increases risk of AD
• Some associations have included
  – Faster rate of decline
  – Increased hippocampal atrophy
  – Psychiatric complications
Acetylcholinesterase Inhibitors (AChEIs)

- Block the enzyme that breaks down acetylcholine into acetate and choline
- Higher concentration of acetylcholine in the synaptic cleft
- Slow rate of decline but do not stop or reverse AD
- Major side effect is gastrointestinal (diarrhea, nausea, vomiting)
• Three main AChEIs on the market:
  ➢ Donepezil
  ➢ Galantamine
  ➢ Rivastigmine

• Donepezil, galantamine, and rivastigmine all approved for treatment of mild-mod AD

• Donepezil and rivastigmine patch also indicated for severe AD
Memantine

- Blocks influx of Ca2+
- Slows rate of decline, does not stop or reverse
- Generally well-tolerated; may cause dizziness, headache, or confusion
- FDA approved for moderate-severe AD
Treatment Algorithm

• General Approach:
  ➢ Start with AChEI for mild-mod AD
  ➢ Add memantine for mod-severe AD

• Memantine may be better tolerated

• None of these medications STOP or REVERSE decline!

• All are frequently used off-label for potential disease-modifying effects in other types of dementia
Vascular Dementia

- Second-most common etiology of dementia (15-30%)

- Related to vascular events in the brain (acute or chronic ischemic injury)

- Suggestive features include:
  - Cerebrovascular disease or evidence on MRI
  - Vascular risk factors
  - Onset correlated with known event
  - “Step-wise” progression of cognitive deficits
  - Heterogeneous sx$s depending on lesion (aphasia, dysarthria, focal weakness…)

Vascular Dementia

Treatment

• Goal to reduce further vascular damage
  ➢ Treat hypertension
  ➢ Treat hyperlipidemia
  ➢ Diet
  ➢ Exercise
Dementia with Body Dementia (DLB)

- Sometimes cited as second most common form of dementia

- Central Feature: progressive cognitive decline

- Core features (need 1-2/3):
  - Fluctuating cognition (resembles delirium)
  - Well-formed, detailed visual hallucinations
  - Spontaneous Parkinsonism
Suggestive Features:
- REM sleep d/o
- Neuroleptic sensitivity
- Low dopamine transporter uptake on imaging

Dementia occurs *before* the onset of Parkinson’s symptoms

May respond to cholinesterase inhibitors
Parkinson’s Disease Dementia (PDD)

- Affects 50% Parkinson’s patients after 10 years, 80% after 20 years
- More common as physical impairments and age increase
- Symptoms VERY similar to DLB
- Distinction is mainly temporal: Parkinson’s symptoms first
- Also see Lewy Bodies on autopsy
• Treatment

- Motor symptoms respond to PD medications
  - Monitor for VH
  - If VH, give lowest effective dose of PD medication, and consider quetiapine or clozapine for psychotic sxs

- May respond to cholinesterase inhibitors
  - Donepezil, galantamine, rivastigmine (patch form)
Frontotemporal Dementia (FTD)

- Degeneration in frontal lobe
- Progressive decline
- 2 main subtypes: behavioral variant and aphasia variant

- Key features:
  - Behavioral (most common): personality change, disinhibited, apathy, loss of empathy
  - Aphasia: severe word-finding difficulty / comprehension difficulty

- Neuropathology: Pick Bodies (tau protein)
<table>
<thead>
<tr>
<th>FTD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset 50’s</td>
<td>Age onset &gt;65</td>
</tr>
<tr>
<td>Memory impairments subtle initially</td>
<td>Memory impairments early and most pronounced</td>
</tr>
<tr>
<td>Language impairments: anomic aphasia, paraphasias, reticence</td>
<td>Language impairments: some anomias, most in later stages</td>
</tr>
<tr>
<td>Early and prominent disinhibition, apathy</td>
<td>Behavior changes in later stages</td>
</tr>
<tr>
<td>Frontal and temporal lobe atrophy</td>
<td>General atrophy, esp. parietal and temporal lobes</td>
</tr>
</tbody>
</table>
Treatment

- Symptomatic
- Focused on behavioral symptoms
- SSRIs
  - Strongest evidence but per clinical/observational report vs. RCT
  - Consider trazodone

Avoid

- Cholinesterase Inhibitors
  - May worsen agitation / aggression
  - No clinical benefit in terms of cognition
- Memantine
  - More frequent adverse cognitive effects than placebo
- Benzodiazepines
  - Paradoxical agitation
Early Diagnosis

- Diagnostic Imaging
- Genetic Testing
- Cerebrospinal Fluid (CSF)
- Blood
Typical FDG-PET Scans in Dementia

Bohnen et al. 2012
Positron Emission Tomography

http://newscenter.berkeley.edu/2012/01/23/engaged-brain-amyloid-alzheimers/
Genetic Testing

Early Onset

• May be helpful if risk factors (e.g., known family history)

Late Onset

• Not currently recommended
• May be a “piece of the puzzle”
Biomarkers: CSF and Blood

CSF

- Amyloid LOWER
- Tau HIGHER

Blood

- Increased
  - Cortisol, insulin-like growth factor binding protein 2, Beta2 microglobulin, vascular cell adhesion molecule 1, CD40, macrophage inflammatory protein 1 alpha, superoxide dismutase, carcinoembryonic antigen, matrix metalloprotein 2, homocysteine

- Decreased
  - Apolipoprotein E, epidermal growth factor receptor, hemoglobin, calcium, zinc, interleukin 17, albumin

Doecke et al. 2012
Amyloid as Drug Target

Immunotherapy

- Purpose to remove amyloid beta 42 protein, thereby reduce toxicity/ neurodegeneration

- Bapineuzumab (humanized N-terminal–specific anti-Aβ monoclonal antibody)
  - Failed to improve functional/cognitive performance
  - High incidence amyloid-related imaging abnormalities (ARIA)

Tayeb et al. 2013
Amyloid as Drug Target
Amyloid as Drug Target

• Solanezumab (humanized analogue of the murine antibody)
  ➢ Targets soluble forms of amyloid beta
  ➢ Secondary analysis—reduction in cognitive decline in AD patients
  ➢ Low risk of ARIA

Tayeb et al. 2013
Amyloid as Drug Target

Synthesis (enzymes)
Aggregation (tramiprosate)
Inflammatory response
Clearance

Kumar et al. 2015
Tau as Drug Target

Tau-neurofibrillar tangles

- Block hyperphosphorylation
- Strengthen microtubules
- Disrupt oligomerization
- Promote degradation
Other Treatment Targets

- Inflammation
- Insulin
- Mitochondrial dysfunction
- Oxidative stress
- Cholesterol
- Hormones
- Metals

Kumar et al. 2015; Li et al. 2006; Bosel et al. 2005; Barron et al. 2006; Manczak et al. 2010; Bush & Tanzi 2008
“What can I do to reduce risk?”

Basic Health Maintenance

• Healthy diet
• Normal range weight
• Regular exercise
• Normal range cholesterol
• Normal range BP
“What can I do to reduce risk?”

- **Keep brain active**
  - Learn new technology
  - Take a class
  - Learn a new game (cards, sport, puzzles…)

- **Stay socially connected**
  - Visit with friends and family
  - Participate in organizations
Thank you!