Alzheimer’s Disease and Related Dementia Disorders

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Mild Cognitive Impairment

- Mild cognitive impairment (usually affecting memory)
- Other cognitive abilities often intact
- No functional disability
- Represents a pre-AD transitional state for many
- Progression to AD occurs more frequently than in normal elderly (~10-15% each year)

Mild Cognitive Impairment

- Mild cognitive impairments predict dementia in non-demented elders.
- Memory loss alone rarely (6%) progresses to dementia over two years.
- Memory loss plus other cognitive impairments does predict conversion to AD:
  - 48% at two years
  - 77% at four years vs 24% of memory only pts.

» Bozoki. *Arch Neurol* 2001;58:411-416
Mild Cognitive Impairment: Subtypes and Putative Etiologies

**Diagram:**
- Mild Cognitive Impairment
  - Cognitive complaint
    - Not normal for age
      - Not demented
        - Cognitive decline
          - Essentially normal functional activities
            - MCI
              - Memory impaired?
                - Yes: Amnestic MCI
                  - Memory impairment only?
                    - Yes: Amnestic MCI Single Domain
                      - No: Amnestic MCI Multiple Domain
                - No: Non-Amnestic MCI
                  - Single non-memory cognitive domain impaired?
                    - Yes: Non-Amnestic MCI Single Domain
                      - No: Non-Amnestic MCI Multiple Domain
    - No: MCI

**Table:**
- Aetiology: Degenerative, Vascular, Psychiatric, Trauma
  - MCI Amnestic
    - AD
    - MCI + Amn Multiple Domain
    - MCI single Nonmemory Domain
  - MCI non-Amn
    - AD
    - VaD
    - Depr
  - DLB
  - FTD
  - Psychiatric
  - Trauma
Mild Cognitive Impairment

- Mild cognitive impairment represents early-stage Alzheimer’s disease

- Prospective clinical and psychometric study of 177 normal elders and 277 MCI followed > 9.5 years
  - 100% of CDR 0.5 progressed to dementia
  - 60% progressed to dementia by 5 years
  - 24/25 patients with CDR 0.5 at post mortem had dementia disorder
    - 21 (84%) had AD

» Morris. *Arch Neurol* 2001;58:397
Normal Aging vs. AD

Start AD brain changes

MCI

Clinically diagnosed AD

Function

Birth 40 60 80 Death

Life Course

Total loss independent function

Normal Aging
Neuropathologic Changes Characteristic of Alzheimer’s Disease

Normal

AD

AP = amyloid plaques.
NFT = neurofibrillary tangles.

Courtesy of Albert Enz, PhD, Novartis Pharmaceuticals Corporation.
Pathology of AD

- There are 3 consistent neuropathological hallmarks:
  - Amyloid-rich senile plaques
  - Neurofibrillary tangles
  - Neuronal degeneration

- These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms
β-amyloid Plaques

Immunocytochemical staining of senile plaques in the isocortex of a brain of a human with AD (anti-amyloid antibody)
Proteolytic Cleavages of Amyloid Precursor Protein Produce A\(\beta\) Peptide

\[\text{\(\beta\)-amyloid precursor protein} \rightarrow \text{A}\(\beta\) peptide} \]

\[\text{\(\beta\)-secretase} \rightarrow \text{Extracellular space} \rightarrow \text{TM} \rightarrow \text{Cytoplasm} \]

Summary of Evidence for the Amyloid Hypothesis

- Presence of β-A4 in amyloid plaques
- Plaques develop years before dementia symptoms
- β-A4 arises from β-APP gene on chromosome 21
- Alzheimer's disease pathology in trisomy 21 (Down syndrome)
- Existence of mutated forms of β-APP gene and protein that cause AD
- Existence of mutated forms of presenilin protein genes on chromosomes 14 and 1 that cause AD
Immunization with Aβ Reduces Aβ Deposition in Hippocampus of Aβ$_{42}$- Injected Mice

- hippocampal Aβ deposition (a,b)
- neuritic plaque formation (c,d)
- cortical astrocytosis (e,f)

Schenk et.al, Nature, 400:173-177, 1999
Experimental Therapies: Amyloid Inhibition

- Secretase inhibitors
  - Beta (BASE): phase 3, safety?
  - Gamma: phase 2 and 3, unsafe, failed
- Aβ modulators (SALA’s)
  - Modulation of gamma secretase
    - Tarenflurbil (Flurizan): phase 3, failed
  - Blocking amyloid fibril formation
    - Transiposate (Alzhemed): phase 3, failed
- Chelators
  - Clioquinol: unsafe, cancelled
- Aβ vaccines
  - Active
    - AN1792: unsafe, cancelled
    - ACC-001: phase 1
  - Passive
    - Specific:
      - Bapineuzumab): phase 3, safety ?, failed
      - Solanezumab: phase 3, efficacy ?
    - Non-specific (IVIG): phase 2/3, failed
Neurofibrillary Tangles

Immunocytochemical staining of neurofibrillary tangles in the isocortex of the brain of a human with AD (anti-tau antibody)
Tau Association With Microtubules

- **Hyperphosphorylated tau subunits**
- **PHF composed of tau subunits**

**Diagram:**
- Tau bound to microtubule
- Microtubule

**Legend:**
- PHF = paired helical filaments.
Apolipoprotein E and AD Pathology

- Apolipoprotein E (APOE) genotype is associated with AD risk
- APOE-epsilon2 may be protective
- APOE-epsilon4 is associated with increased risk
- The role of APOE-epsilon2 and APOE-epsilon4 in pathogenesis is not known
- APOE is found in β-amyloid plaques and neurofibrillary tangles and may affect protein interactions
Fig 1. Alzheimer disease (AD) undoubtedly has multiple causes. ApoE4 may independently and directly cause AD in response to a variety of “second hits.” ApoE4 = apolipoprotein E4; Aβ = amyloid-beta; APP = amyloid precursor protein.
Cholinergic System Innervates Areas Associated With Memory

FC = Frontal cortex
PC = Parietal cortex
OC = Occipital cortex
H = Hippocampus
B = Nucleus basalis
S = Medial septal nucleus

The most prominent neurotransmitter abnormalities are cholinergic

- Reduced activity of choline acetyltransferase (synthesis of acetylcholine)\(^1\)

- Reduced number of cholinergic neurons in late AD (particularly in basal forebrain)\(^2\)

Cholinergic Hypothesis

- Acetylcholine (ACh) is an important neurotransmitter in areas of the brain involved in memory formation.
- Loss of ACh activity correlates with the severity of AD.

Normal Cholinergic Function

ACh = acetylcholine; AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; ChAT = choline acetyltransferase; CoA = coenzyme A.

# Cholinesterase Inhibitors: General Overview

<table>
<thead>
<tr>
<th></th>
<th>Tacrine</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Available</strong></td>
<td>1993</td>
<td>1996</td>
<td>2000</td>
<td>2001</td>
</tr>
<tr>
<td><strong>Brain Selectivity</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes (brain-region selective)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>Reversible</td>
<td>Reversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Chemical Class</strong></td>
<td>Acridine</td>
<td>Piperidine</td>
<td>Carbamate</td>
<td>Phenanthrene alkaloid</td>
</tr>
<tr>
<td><strong>Enzymes Inhibited</strong></td>
<td>AChE Yes</td>
<td>AChE Yes</td>
<td>AChE Yes</td>
<td>AChE Yes</td>
</tr>
<tr>
<td></td>
<td>BuChE Yes</td>
<td>AChE Negligible</td>
<td>AChE Yes</td>
<td>AChE Negligible</td>
</tr>
</tbody>
</table>

AChE = acetylcholinesterase; BuChE = butyrylcholinesterase.
Neurotransmitter Deficiencies in AD

- Nucleus basalis of Meynert (acetylcholine)
- Locus ceruleus (norepinephrine)
- Raphe nuclei (serotonin)
Mild Cognitive Impairment

• Upregulation of ChAT activity could be important factor preventing the transition of MCI persons to AD.

• ChAT levels in MCI and AD
  - parietal cortex: reduced only in severe AD
  - superior frontal cortex
    - increased in MCI
    - unchanged in normals and mild AD
  - hippocampus
    - also increased in MCI compared to normals and mild AD

» DeKosky. *Ann Neurol* 2002;51:145
The Mild Cognitive Impairment Study

Table 3. Hazard Ratios for the Risk of Progression to Alzheimer’s Disease in the Donepezil and Vitamin E Groups as Compared with the Placebo Group.*

<table>
<thead>
<tr>
<th>Interval</th>
<th>All Subjects</th>
<th>APOE ε4 Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Donepezil vs. placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 mo</td>
<td>0.42 (0.24–0.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.64 (0.44–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>0.80 (0.57–1.13)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vitamin E vs. placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 mo</td>
<td>0.83 (0.52–1.32)</td>
<td>0.43</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.95 (0.67–1.36)</td>
<td>0.79</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>1.02 (0.74–1.41)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval. P values were not adjusted for multiple comparisons. In the donepezil group, when corrected for multiple comparisons, the P value at 24 months for all subjects became nonsignificant (P=0.052), and the P value at 36 months for APOE ε4 carriers also became nonsignificant (P=0.078).
Pathophysiologic Hypothesis of AD

- β-Amyloid
- Glutamate
- Excitotoxicity
- Neurofibrillary Tangles
- Other Factors
  - Inflammation
  - Mitochondrial Dysfunction
- Cell Damage/ Loss (ACh deficit)
- Dementia
# Memantine Pivotal Trials in Moderate to Severe AD

<table>
<thead>
<tr>
<th>Study Design</th>
<th>First-Line Therapy in Moderate to Severe AD&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Combination Memantine and Donepezil&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Nursing Home Patients With Dementia&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine dose</td>
<td>10 mg bid</td>
<td>10 mg bid (plus donepezil)</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Duration in weeks</td>
<td>28</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>MMSE range</td>
<td>3-14</td>
<td>5-14</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

**Principal Efficacy Measures**

<table>
<thead>
<tr>
<th>Category</th>
<th>Measure</th>
<th>Measure</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global change</td>
<td>CIBIC-Plus</td>
<td>CIBIC-Plus</td>
<td>CGI-C</td>
</tr>
<tr>
<td>Cognition</td>
<td>SIB</td>
<td>SIB</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>ADCS-ADL&lt;sub&gt;19&lt;/sub&gt;</td>
<td>ADCS-ADL&lt;sub&gt;19&lt;/sub&gt;</td>
<td>BGP-Care</td>
</tr>
</tbody>
</table>

Sources:
Diagnosis of Alzheimer’s Disease: NINCDS/ADRDA Criteria

1. In academic referral centers the accuracy of the diagnosis of probable AD is 81-100%.
   - Galasko et al, 1994
   - Morris et al, 1988
   - Tierney, 1988

2. In one post mortem series, 77% of cases of possible AD had AD.
   - Galasko et al, 1994

3. In a community based post mortem series, the accuracy of the diagnosis of probable AD was 75%.
   - Lim et al, 1999
AD Is Often Misdiagnosed

Patient initially diagnosed with AD

- Yes 28%
- No 72%

Patient's first diagnosis other than AD

- Dementia (not AD): 35%
- Depression: 14%
- Stroke: 9%
- No diagnosis: 7%
- Other: 21%

Source: Consumer Health Sciences, LLC. Alzheimer's Caregiver Project. 1999.
AD Is Underdiagnosed

- Early AD is subtle; the initial signs and symptoms are easily missed
- Less than half of AD patients are diagnosed
- Undiagnosed AD patients face unnecessary added social, financial, and medical problems
- Early diagnosis and appropriate intervention may lessen disease burden

Diagnosis of Alzheimer’s Disease: MRI Volumetry
Hippocampal volume is a sensitive and specific indicator of neuropathology, regardless of the presence or absence of cognitive impairment (Nun Study)*

- predicted AD neuropathologic criteria for all cases
  - 24 demented sisters
  - 32 non-demented sisters
    - 8 sisters with mild memory impairment
    - 24 sisters with intact memory

The Mild Cognitive Impairment MRI Study

Figure 2. Current MCI Trial Results Examining Time to Conversion to AD by Baseline Hippocampal Volume Tertiles

- RR for Highest Tertile = 0.30 (CI: 0.13 - 0.93)
- RR for Middle Tertile = 0.45 (CI: 0.21 - 0.97)
Diagnosis of Alzheimer’s Disease: PET and SPECT

Typical AD PET Scan

Provided courtesy of M. Mega, MD, PhD, Department of Neurology, UCLA School of Medicine.
Diagnosis of Alzheimer’s Disease: SPECT

Therapeutics and Technology Assessment Subcommittee of the AAN

- SPECT can be considered an established technique to support the clinical diagnosis of AD.
- PPV = 87-100% in post-mortem series
  - Read et al, 1995
  - Bonte et al, 1997
  - Risberg et al, 1997
Diagnosis of Alzheimer’s Disease: SPECT

- Diagnostic pattern is bilateral reduction of temporoparietal cortical perfusion
- Most common cause of false positives is Parkinson’s disease and related syndromes
- Sensitivity in clinical series relatively low
  - Average = 79% (range 29-100%)
  - True positives higher in more advanced disease
    - Mild = 40-70% vs severe = 80-90%
  - 20% of AD patients show unilateral defects
Human Amyloid PET Imaging
AV-45 (florbetapir F18)

Clark C. JAMA 305:275-283, 2011
Human Amyloid PET Imaging
AV-45 (florbetapir F18)

Phase 3 histopathology study
- 35 subjects expected to die < 6 months
  - 18/19 (97%) of AD subjects positive scan
  - 0/16 normal subjects positive scan
- 74 young (18-50) normal subjects
  - All 74 amyloid negative

Phase 2 studies
- Positive scan predicts conversion from MCI to AD over 2-4 years

FDA approval to estimate amyloid plaque density: April 10, 2012
- Not covered by insurance
  - Centers for Medicare & Medicaid Services (CMS) meeting 1/30/13 concluded low to intermediate confidence that amyloid PET results affect health outcomes; recommended only coverage with evidence development on July 3rd

References:
This study is designed to determine the effectiveness of florbetapir (18F) in changing patient management and to evaluate the association between scan status and cognitive decline.

N=600

Timeline: October 2012 to December 2014

Primary Outcome Measures:

- Patient Management
  - Comparison of the proportion of patients who have a change in management from baseline to 3 months for patients who receive scan results immediately (intervention arm) and those who receive scan results 12 months later (control arm).

- Patient Prognosis
  - Association between scan status and cognitive decline.
Genetic mutations account for 45-90% of early onset familial AD cases, i.e. age <65

- PS-1 mutations in 30-70% of patients
- PS-2 account for another 5%
- APP account for another 10-15%

High PPV, assumed to be 100% for eventual development of AD

Pre and post test genetic counseling, education, and support necessary for asymptomatic positives
Diagnosis of Alzheimer’s Disease: Apolipoprotein E Genotype

Athena

+ in 44-64% of AD cases
an e4 allele indicates a 97% PPV in persons with dementia that AD is a contributing cause. Therefore, the presence of the e4 allele usually rules out other causes of dementia.

absence of an e4 allele does not rule out AD
results cannot be interpreted for asymptomatic persons, therefore, our policy is not to test asymptomatic individuals.
Diagnosis of Alzheimer’s Disease: CSF Aβ42 and Tau

With appropriate cutoffs, low Aβ42 and high tau levels in CSF support diagnosis of AD vs. normal elders with a sensitivity of 77% and specificity of 90%

- many cases in non-diagnostic range
- positives may be useful in distinguishing early AD from normal aging
- 26/74 (35%) of cases with other neurological disorders classified as AD
  - high risk of false + in clinical practice
  - awaiting post mortem information

When AT index in AD range, phospho-tau discriminates AD from FTD and DLB

- Sensitivity 72-85%; specificity 74-85%

Consensus Report of the Working Group on: Molecular and Biochemical Markers of Alzheimer’s Disease

- Regan Research Institute of the Alzheimer Association
- National Institute on Aging Working Group

For suspected early-onset familial AD it is appropriate to search for mutations e.g. presenilin 1

For late-onset and sporadic AD

- ApoE e4 can add confidence to the clinical diagnosis
- Among other proposed markers, CSF Ab$_{42}$ and tau come closest to fulfilling criteria for a useful biomarker

Alzheimer's Association and NIH Revised Diagnostic Criteria

**Alzheimer's Disease**
- Probable diagnosis is "enhanced" by
  - Documented cognitive decline
  - Biomarkers
    - MRI volumes
    - PET
    - CSF a-beta, tau
  - Mutation carrier status
- Definite AD: post mortem

**Mild Cognitive Impairment**
- Topographic + molecular biomarker positivity "strongly" supports AD
- Topographic or molecular biomarker alone provides intermediate support for AD

**Preclinical Alzheimer's Disease**
- Stage 1: asymptomatic cerebral amyloidosis
- Stage 2: cerebral amyloidosis + other biomarker(s)
- Stage 3: stage 2 + subtle cognitive decline (pre-MCI)

Alzheimers Dement. 2011 May;7(3)
Differential Diagnosis of Dementia

Vascular dementias
- Multi-infarct dementia
- Binswanger’s disease

Vascular dementias and AD

Dementia with Lewy bodies
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD

AD and dementia with Lewy bodies

Other dementias
- Frontal lobe dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Many others

AD and dementia with Lewy bodies

Vascular Dementia

- Second or third most common cause of dementia
- Affects 5.2% of the population over 90 years of age
- Associated with:
  - Stroke
  - Cerebrovascular disease
- Often coexists with AD and may share common pathology
- Causes decline in cognition, function, and behavior
## Frequency of VaD in Dementia Autopsy Series

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>VaD± (Pure)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brun 1994 (175)</td>
<td>70% (34%)</td>
<td>Dem Study</td>
</tr>
<tr>
<td>Galasko 1994(170)</td>
<td>9% (2%)</td>
<td>AD Res Ctrrs</td>
</tr>
<tr>
<td>Drach 1997 (59)</td>
<td>27% (12%)</td>
<td>Nursing Home</td>
</tr>
<tr>
<td>Nolan 1998 (87)</td>
<td>37% (0%)</td>
<td>Dem Clinic</td>
</tr>
<tr>
<td>Lim 1999 (134)</td>
<td>34%+ (3%)</td>
<td>Dem Register</td>
</tr>
<tr>
<td>Duara 2000 (307)</td>
<td>16% (4%)</td>
<td>Brain Bank</td>
</tr>
</tbody>
</table>
Mixed Pathology in AD & VaD
State of Florida Brain Bank (n=307)

Alzheimer's Disease
- Pure: 64%
- +DLB: 21%
- +VaD: 13%
- +Oth: 2%

Vascular Dementia
- Pure: 27%
- +AD: 63%
- +Oth: 10%
Dementia With Lewy Bodies

- 15%ï 25% of all dementia in the elderly
- Onset ~75ï 80 years
- Duration ~3.5 years (<1ï 20)
- Characterized by
  - Fluctuating cognitive impairment (~80%)
  - Recurrent visual hallucinations (>60%)
  - Parkinsonism (65%ï 70%)
- Cortical and brainstem Lewy bodies ± AD pathology
  - Alpha-synuclein inclusions

Dementia With Lewy Bodies

Supportive Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient loss of consciousness</td>
<td>40%</td>
</tr>
<tr>
<td>Falls and syncope</td>
<td>50%</td>
</tr>
<tr>
<td>Systematized delusions</td>
<td>70%</td>
</tr>
<tr>
<td>Neuroleptic sensitivity</td>
<td>50%</td>
</tr>
<tr>
<td>Depression</td>
<td>30-50%</td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
<td>25%</td>
</tr>
</tbody>
</table>

DLB is underdiagnosed and may constitute 15-25% of all dementias
Dementia With Lewy Bodies

- Presence of dementia, gait/balance disorder, prominent hallucinations and delusions, sensitivity to traditional antipsychotics, and fluctuations in alertness

- Neuropsychologic tests do not reliably differentiate DLB from either AD or VaD

- Patients with DLB show less temporal lobe atrophy on MRI and more hypoperfusion on SPECT and PET in the occipital lobes than do patients with AD

- Neuroimaging, however, has not proven successful in differentiating DLB from AD

Neuropsychiatric Symptoms in DLB vs AD

*P<.05
Effects of Rivastigmine on Behavioral Symptoms in DLB

NPI 10-Item Score

Weeks

Baseline

12

20

Mean Change from Baseline

Rivastigmine

Placebo

NPI 10-Item Score—Percentage of Patients Improving by ≥30% from Baseline

Patients Improving (%)

Week 20

*P<.01 vs placebo; **P<.001 vs placebo

†Responder definition recommended by NPI author (J Cummings)

PD and Dementia

- At least one-third of PD patients develop dementia.
- Patients with PD have degeneration of the nucleus basalis of Meynert and low brain ChAT levels.
- The dementia of PD is not improved by dopaminomimetic drugs.
- ChE inhibitor therapy in PD may be beneficial.

Frontotemporal Dementia

- FTD is the most common of the neurodegenerative syndromes produced by frontotemporal lobar degeneration, and is less common than AD, VaD, and DLB.

- FTD is characterized more by the pattern of behavioral deficits than by neuropsychological impairment.

Frontotemporal Dementia
Pick Body
**Clinical features of FTD include decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and impersistence, hyperorality and dietary changes, perseverative and stereotyped behavior, and wandering.**

**Current treatment options only address symptomatic management, and there is no evidence for the use of AChEIs in this condition.**

- Serotonin deficit may relate to behavior

**Supportive role of neuroimaging**
Functional Imaging
(PET/SPECT)

Pick’s Disease
MRI: Frontotemporal Dementia

Notice that the areas circled in red have less white area compared with the other areas. This indicates loss of brain tissue (atrophy).
Overlap Dementia Syndromes

Figure

- Hemorrhagic strokes
- AD
- FTLD
- Pathologic phenotype:
  - Aβ
  - CAA
  - CAA+AD
  - AD
  - FTLD-tau
  - FTLD-U
- Genotype:
  - APP
  - PSEN1/2
  - MAPT
  - PGRN
Evolving Nosology of “Dementia” Disorders

- Dementia: A word to be forgotten
- Molecular, imaging, and behavioral observations will define disease in the future

Genetic/Environmental factors: tests

Pathologic changes in brain: brain imaging/CSF

Change over time: preclinical diagnosis

Topographic variations: brain imaging

Behavioral and cognitive syndromes: History & exam

DSM-V Criteria for Major Neurocognitive Disorder

- Evidence of significant cognitive decline from a previous level of performance in one or more of the cognitive domains based on:
  - Reports by the patient or a knowledgeable informant, or observation by the clinician, of clear decline in specific abilities in specific domains.
  - AND
  - Clear deficits in objective assessment of the relevant domain (typically > 2.0 SD below the mean [or below the 2.5th percentile] of an appropriate reference population)

- The cognitive deficits are sufficient to interfere with independence (e.g., at a minimum requiring assistance with instrumental activities of daily living, i.e., more complex tasks such as finances or managing medications)

- The cognitive deficits do not occur exclusively in the context of a delirium

- The cognitive deficits are not wholly or primarily attributable to another Axis I disorder
DSM-V Criteria for Minor Neurocognitive Disorder

- Evidence of minor cognitive decline from a previous level of performance in one or more cognitive domains based on:
  - Reports by the patient or a knowledgeable informant, or observation by the clinician, of minor levels of decline in specific abilities as outlined for the specific domains above. Typically these will involve greater difficulty performing these tasks, or the use of compensatory strategies.
  - Mild deficits on objective cognitive assessment (typically 1 to 2.0 SD below the mean [or in the 2.5th to 16th percentile] of an appropriate reference population (i.e., age, gender, education, premorbid intellect, and culturally adjusted).
  - When serial measurements are available, a significant (e.g., 0.5 SD) decline from the patients’ own baseline would serve as more definitive evidence of decline.

- The cognitive deficits are not sufficient to interfere with independence (Instrumental Activities of Daily Living are preserved), but greater effort and compensatory strategies may be required to maintain independence.

- The cognitive deficits do not occur exclusively in the context of a delirium.

- The cognitive deficits are not wholly or primarily attributable to another Axis I disorder.
What about treatment?
Name FDA approved indication for dementia severity of each drug

- **Aricept (Donepezil)**
  - Mild, moderate, severe
- **Razadyne (Galantamine)**
  - Mild, moderate
- **Exelon (Rivastigmine)**
  - Mild, moderate
- **Namenda (Memantine)**
  - Moderate, severe
Combination Rx with cholinesterase inhibitor and memantine

- Shown effective in mild to moderate AD
- Shown effective in moderate to severe AD
- Shown effective for all stages of AD
- Not any more effective than monotherapy for AD
Recommendations for Best Practices: Algorithm

**Screen**
all elderly patients with a memory complaint*

**Diagnose and treat**
- Evaluate cognition, function, and behavior
- Treat at time of diagnosis

**Perform**
on-going monitoring and evaluation

**Mild**
- Treat with ChEI

**Moderate**
- Treat with combination ChEI + memantine

**Severe**
- Treat with memantine, add an approved ChEI as needed

**Reevaluate**
within 2 months and monitor every 6 months

**Counsel**
patients and caregivers about treatment expectations

**Consider**
potentially reversible causes of cognitive and/or functional impairment if a patient currently on antidementia therapy is showing signs of rapid decline†

**Provide**
geriatric care management and counseling and refer patients and caregivers to AD support groups

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*Memory complaint may be raised by family or caregiver; all patients ≥75 years of age should be screened regardless of clinical presentation.
†Possible causes include medical comorbidities, the effects of other drugs, behavioral disturbances, or delirium.
Which drug is approved for treatment of Parkinson’s disease related dementia?

- Donepezil
- Galantamine
- Rivastigmine
- Memantine
Which drug(s) shown effective in clinical trials for the treatment of Dementia with Lewy bodies?

- Rivastigmine
- Galantamine
- Donepezil
- Memantine
Effects of Rivastigmine on Behavioral Symptoms in DLB


*P<.01 vs placebo; **P<.001 vs placebo

†Responder definition recommended by NPI author (J Cummings)
Clinical Trial: Donepezil for Dementia with Lewy Bodies

- 142 subjects, randomized, placebo controlled, 12 weeks

- Efficacy for
  - MMSE
  - Global function: CIBIC+
  - Behavior: NPI
    - Delusions
    - Hallucinations
    - Fluctuating cognition
  - Caregiver burden

Memantine for DLB and PD

- 199 subjects, randomized, placebo controlled, 24 weeks

- Efficacy, only in DLB, for
  - Face recognition, Stroop interference
  - Global function: CGIC
  - Behavior: NPI
    - Delusions
    - Hallucinations
    - Sleep & eating

- No efficacy for IADLs, CG burden

What statement is true regarding treatment of mild cognitive impairment?

- Cholinesterase inhibitors are effective in treating cognitive deficits of MCI
- Donepezil was shown to reduce progression to dementia over 3 years in ApoE-E4 positive subjects
- Vitamin E was shown to reduce progression to dementia over 3 years in ApoE-E4 positive subjects
- All of the above
### Table 3. Hazard Ratios for the Risk of Progression to Alzheimer's Disease in the Donepezil and Vitamin E Groups as Compared with the Placebo Group.*

<table>
<thead>
<tr>
<th>Interval</th>
<th>All Subjects</th>
<th></th>
<th>APOE ε4 Carriers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Donepezil vs. placebo</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>First 12 mo</td>
<td>0.42 (0.24–0.76)</td>
<td>0.004</td>
<td>0.34 (0.16–0.69)</td>
<td>0.003</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.64 (0.44–0.95)</td>
<td>0.03</td>
<td>0.54 (0.35–0.86)</td>
<td>0.009</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>0.80 (0.57–1.13)</td>
<td>0.21</td>
<td>0.66 (0.44–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Vitamin E vs. placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 12 mo</td>
<td>0.83 (0.52–1.32)</td>
<td>0.43</td>
<td>0.78 (0.46–1.34)</td>
<td>0.37</td>
</tr>
<tr>
<td>First 24 mo</td>
<td>0.95 (0.67–1.36)</td>
<td>0.79</td>
<td>0.95 (0.64–1.41)</td>
<td>0.79</td>
</tr>
<tr>
<td>All 36 mo</td>
<td>1.02 (0.74–1.41)</td>
<td>0.91</td>
<td>0.95 (0.66–1.36)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval. P values were not adjusted for multiple comparisons. In the donepezil group, when corrected for multiple comparisons, the P value at 24 months for all subjects became nonsignificant (P=0.052), and the P value at 36 months for APOE ε4 carriers also became nonsignificant (P=0.078).
Medical food approved for treatment of AD?

- Medium chain triglyceride shake
- Folic acid
- Vitamin E in high dosage
- Gingko Biloba
- Omega 3 fatty acids
Axona®

- Medium chain triglycerides converted to ketones
- Alternative energy source for neurons not adequately utilizing glucose
  - AD is type 3 diabetes
- Symptomatic benefit seen only in ApoE4- subjects in one 3-month trial
Black box warning re: mortality risk of antipsychotics in elderly dementia patients

- Applies only to newer "atypical" drugs
- Applies only to older drugs
- Includes risk due to neuroleptic malignant syndrome
- Includes risk due to diabetes
- Includes risk due to cardiovascular problems, including sudden death
Black Box Warning

Conventional Antipsychotics: Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Molindone, Perphenazine, Pimozide, Prochlorperazine, Thioridazine, Thiothixene, Trifluoperazine

*Increased Mortality in Elderly Patients with Dementia Related Psychosis*

- Elderly patients with dementia related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.
- Analyses of seventeen placebo controlled trials (modal duration of 10 weeks, largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug treated patients of between 1.6 to 1.7 times that seen in placebo treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group.
- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.
- Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.
- The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
- This drug is not approved for the treatment of patients with dementia-related psychosis (See WARNINGS in package insert).
Which antidepressant was shown possibly effective in treating FTD?

- Sertraline
- Citalopram
- Imipramine
- Venlafaxine
- Trazodone
DB, PC Randomized Trials in bvFTD

Å Paroxitene

- Potent SSRI with mild anticholinergic effects
- DB, PCC, 40 mg, 6 weeks
  - Worse cognition and no effect on behavior
  - Non significant trend toward increase in behavioral problems on NPI

Å Trazodone

- Weak serotonin agonist, adrenergic and histaminic blocker
- DB, PC, crossover trial, 26 patients, 300 mg daily
  - Significant decrease in NPI score, by >50%
    - Improvement in irritability, agitation, depressive symptoms and eating disorders
  - No adverse effect on MMSE
  - Half experienced fatigue, dizziness, hypotension or cold extremities

Questions?