Best Practices in Mild Cognitive Impairment & Dementia

Bruce L. Miller, MD
A.W. and Mary Margaret Clausen Distinguished Professor in Neurology
Director, Memory and Aging Center
Joint Appointment in Psychiatry
UCSF School of Medicine
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Criteria for Dementia

Cognitive or behavioral symptoms that:
- interfere with usual function
- represent a decline from previous levels of performance
- are not explained by delirium or major psychiatric disorder

Cognitive impairment is measured through
1. history taking from the patient and knowledgeable informant
2. objective cognitive testing
Women & Alzheimer’s Disease

- 5 million Americans live with AD - ¾ are women
- ⅔ of Alzheimer’s caregivers are women, many will have to take time off or resign from their jobs.
- After 60, a woman has 1 in 6 chance develop AD.
- By 2050, 16 million in US ,135 million worldwide will have dementia, and millions more family members and friends will suffer alongside those diagnosed.

Women’s Alzheimer’s Movement
thewomensalzheimersmovement.org

Today 5.3 million Americans aged 65+ years living with dementia; cost of $220B/y

By 2050, dementia population will nearly triple to 13.8 million; cost of $1.160 trillion/y

Dementia is Expensive

<table>
<thead>
<tr>
<th>Average Annual Per Person Medicare Spending</th>
<th>Average Annual Per Person Medicaid Spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seniors without Alzheimer’s Disease and Other Dementias</td>
<td>$7,223</td>
</tr>
<tr>
<td>Seniors with Alzheimer’s Disease and Other Dementias</td>
<td>$23,497</td>
</tr>
<tr>
<td>Seniors without Alzheimer’s Disease and Other Dementias</td>
<td>$3,497</td>
</tr>
<tr>
<td>Seniors with Alzheimer’s Disease and Other Dementias</td>
<td>$8,182</td>
</tr>
</tbody>
</table>


Dementia is Expensive

| Treatable Causes |
| neurodegenerative causes |
| Alzheimer’s disease |
| frontotemporal dementia |
| Lewy body disease |
| and more |

| Neurodegenerative Causes |
| medications |
| metabolic abnormalities |
| nutritional deficiencies |
| emotional problems |
| infection |
| hydrocephalus and more |

Dementia

cognitive decline that interferes with everyday functioning
memory, executive, behavioral, and/or motor symptoms
Dementia Risk Factors

- Head trauma
- Stroke
- Hypertension
- Diabetes
- Poor sleep
- Low cognitive reserve
- Pollution (?)

- Cholesterol
- Homocysteine
- Low exercise
- Specific genes
- Social isolation
- Hearing loss

Models of Degenerative Dementia

All degenerative dementias have:
- Genetic and sporadic form
- Cell culture and animal model
- Preclinical, early symptomatic and symptomatic phase
- Abnormal protein aggregation
- Proteins spread from cell to cell

Neuropathologic Inclusions

<table>
<thead>
<tr>
<th>AD</th>
<th>Aβ-42 &amp; tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTD</td>
<td>tau or TDP-43</td>
</tr>
<tr>
<td>PSP, CBD</td>
<td>tau</td>
</tr>
<tr>
<td>PD, DLB, MSA</td>
<td>α-synuclein</td>
</tr>
<tr>
<td>CJD</td>
<td>PrPsc</td>
</tr>
</tbody>
</table>

Neuropathology Inclusions

- Frontotemporal dementia: Pick body (tau, 1990), ubiquitin (TDP43, 2006), ubiquitin (FUS, 2009), C9 (2011)
- Parkinson dementia, dementia with Lewy bodies (α-synuclein, 1998)
 Tau Spreads Like a Prion

Courtesy of Marc Diamond

Functional Connectivity Dorsal Midbrain Tegmental Network & Tau PET in PSP


Differing Anatomy Defines Dementias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Imaging Anatomy</th>
<th>1st Symptom</th>
<th>Spared</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Hippocampus posterior temporal-parietal</td>
<td>Memory, naming, visuospatial</td>
<td>Social behavior, Movement</td>
</tr>
<tr>
<td>FTD</td>
<td>Frontal (emotional &gt; cognitive neocortex)</td>
<td>Apathy, behavior</td>
<td>Navigation, memory</td>
</tr>
<tr>
<td>DLB</td>
<td>Amygdala temporal-occipital</td>
<td>Movement, hallucinations, visuospatial</td>
<td>Behavior, memory</td>
</tr>
</tbody>
</table>

MCI Across Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Early Deficit</th>
<th>Early Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Memory, Spatial, Language</td>
<td>Social (sometimes language)</td>
</tr>
<tr>
<td>bvFTD</td>
<td>Behavior, Executive</td>
<td>Spatial, Language</td>
</tr>
<tr>
<td>PPA</td>
<td>Language</td>
<td>Spatial, Social</td>
</tr>
<tr>
<td>PD/PDD</td>
<td>REM behavior Autonomic</td>
<td>Social, Memory</td>
</tr>
<tr>
<td>DLB</td>
<td>Movement, Delirium</td>
<td></td>
</tr>
</tbody>
</table>

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[ADD PRESENTATION TITLE: INSERT TAB > HEADER & FOOTER > NOTES AND HANDOUTS]
Psychiatric Changes in Dementia

Molecular Changes Underlying AD

Shdo, et al., submitted

Bateman et al., NEJM 2012

Amyloid Deposition in Autosomal Dominant AD

Research Criteria for Alzheimer's Disease

- At least two of the following:
  - Impairment in ability to remember new information
  - Impaired reasoning ability manage complex tasks
  - Impaired visuospatial abilities
  - Impaired language functions (speak, read, write)
  - Changes in behavior, personality or comportment
  - Insidious onset of decline and progressive worsening of symptoms and function
  - Evidence of a causative genetic mutation
  - Biomarkers for amyloid deposition
Amyloid PET vs. CSF Aβ

Landau et al, Ann Neurol 2013

Amyloid vs. FDG-PET in Differential Diagnosis of AD vs. FTD

AD (N=62, age 65, MMSE 22)
FTD (N=45, age 65, MMSE 22)
Amyloid (PIB) PET visual reads
90% sensitivity, 83% specificity
Inter-rater agreement κ=0.96

FDG-PET visual reads
78% sensitivity*, 84% specificity
Inter-rater agreement κ=0.72*

70 autopsy-proven cases
PIB: Sensitivity 96%, Specificity 88%
FDG: Sensitivity 88%, Specificity 89%

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning
IDEAS-Study@acr.org
IDEAS-Study.org

• National, open-label study on clinical utility of amyloid PET in ~18,500 Medicare beneficiaries with MCI or dementia of uncertain cause
  • Eligible patients referred for PET by dementia experts
  • Scans covered by CMS, performed and interpreted locally
• Aim 1: Impact of scan on management plan at 3 months
• Aim 2: Impact on major medical outcomes at 12 months

The primary hypothesis is that, in diagnostically uncertain cases, amyloid PET will lead to significant changes in patient management, and this will translate into improved medical outcomes

T807 Tau PET in AD

Healthy Very Mild AD Mild AD Severe AD
Tau PET: The New Frontier

Amyloid, tau & brain metabolism
57 year-old AD

Brain dysfunction correlates with tau but not amyloid

Treatable Disorders That Present with Cognitive or Behavioral Problems

- B12 deficiency
- Thyroid deficiency
- Medication side effects
- Depression
- Alcohol or drug dependency
- Cerebrovascular disease
- Autoimmune diseases
- Sleep disorders

What Can We Do?

Principles

- Behavioral, cognitive, motor alterations represent change in the brain
- Some changes are progressive & untreatable, others have treatable component
- Insight not invariably present in the patient or in their loved ones
- “Do no harm”—*not* intervening can harm
- Decisions around intervention rarely clear and can be heart-wrenching
Modifiable Risk Factors Affect Aging

Adiposity & Obesity
Vascular Risk Factors
Chronic Inflammation
Physical Exercise

Physical Exercise

- Physically active women show lower likelihood of cognitive impairment in late life
- Individuals active later in life also showed lower risk than those who were never active

Middleton et al. JAGS 2010

Physical Exercise and BDNF

Exercise induces BDNF

Physical Exercise and BDNF

Physical Exercise and BDNF

What Current Models Lack

Current care models leave gaps leading to

- Lack of caregiver support
- Lack of advance planning
- Lack of community service access & coordination
- Failure to identify med hazards
- Lack of access to dementia expertise

Note: even advanced care models with nurse case management suffer from these gaps; this includes most health plans, Medicare Advantage Plans, and Medicaid Managed Care Providers
Patients and caregivers can reach their specialists from anywhere – as long as they have a phone.

Care Ecosystem Protocols and Services

- Caregiver support & education: Emotional support, behavioral tricks of the trade in dementia care
- Medication reconciliation & coaching: Multiple meds; lack of adherence is common
- Facilitating access to community services: Meals-on-wheels, day care, spiritual support, etc.
- Planning for future medical decision making: Healthcare POA, financial, legal, physical environment
- Access to expert review: Nearly all med lists can be improved; access to dementia specialists for special situations

The Care Ecosystem Navigator

- The navigator role can be integrated into nurse case management & chronic disease management services
- The navigator role can be centralized, based in primary care (PCMH) or both
- The navigator role can be segmented and shared: RN, LPN, MA & layperson allowing top-of-license focus
- The navigator’s caregiver-support role is trust-based and needs to be consistent
Tablet-based Cognitive Assessments

- Tablet-based cognitive screening tools
- Brief form (5–7 minutes) sensitive to mild brain health problems
- Longer form (30 minutes) supports differential diagnosis
- Automated scoring and feedback
- Four alternate forms for repeat testing
- Suitable across education & literacy levels, and different languages & cultures

We now have the basic framework programmed so that we can develop tablet versions of any cognitive tests we want at the MAC.

TabCAT is most accurate at identifying mild cognitive impairment (MCI)

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<th>MMSE</th>
<th>MoCA</th>
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<tr>
<td>Specificity</td>
<td>Sensitivity</td>
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</tr>
<tr>
<td>Normal v. MCI</td>
<td>0.97</td>
<td>0.74</td>
<td>0.93</td>
</tr>
<tr>
<td>Normal v. AD</td>
<td>1.00</td>
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Greater Specificity ✓
- More accurately classifies normals as normal
Greater Sensitivity ✓
- More accurately classifies MCIs as MCI

Possin et al JAGS accepted

TabCAT is most accurate at identifying Alzheimer's dementia (AD)

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Greater Sensitivity ✓
- More accurately classifies ADs as AD
Diagnosis

- History with patient and caregiver – first symptom, pattern of decline, functional status, fluctuation (seizure?)
- Cognitive assessment
- Medical, neurological examination
- Blood work – electrolytes, thyroid, B12
- Image

Treatment

- AD – cholinesterase inhibitor
- Moderate AD consider adding namenda
- FTD – consider antidepressant
- Parkinson dementia – rivastigmine (patch)
- Consider research trial

Clinical Trials at UCSF

**AD**

- Phase 2 crenezumab (monoclonal antibody)
- Phase 2A levetiracetam
- Phase 3 aducanumab

**Tau**

- Phase 1 TPI-287 (AD, CBD & PSP)
- Phase 3 LMTM (bvFTD)
- Phase 1 salsalate (PSP)
- Phase 1 plasma transfusion (PSP)
- Phase 1b BMS-986186 (PSP)
- Phase 1 C2N-8E12 antibody (PSP)

**Progranulin**

- Phase 2a histone deacetylase inhibitor FRM-0534 (FTD-GRN)
- Phase 1 nimodipine (FTD-GRN)
Tau PET Correlates of Cognition in AD (N=40, Mean MMSE 22.2)

Care Ecosystem Modules

Medications
Review and monitor patient medicines to make sure they are safe and effective

Caregiver Support
Offer suggestions and advice about caring for the patient and provide customized caregiver education, support, and community resources

Behavior
Coach and advise caregiver on strategies to manage behaviors while promoting safety and quality of life

Decision-Making
Provide support and resources for medical, legal, and financial care planning

Care Ecosystem in an Integrated Delivery System or Network: Overview

- Opportunity to reduce ER, Inpatient, SNF and skilled HH (& LTC if applicable) costs
- Targeted at financially at-risk populations – ACOs, MA, Medicaid managed care
- Care Ecosystem functions can be integrated into existing operations
- Care Ecosystem fits most competitive strategies
- Care Ecosystem fits payer/compliance trends