Evaluation & Management of Dementia: Improving Care

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Disclosures

- None
Mild Cognitive Impairment: Decline without significant impact on social or professional life.

Dementia: “The acquired decline of cognitive abilities sufficient to result in social or occupational impairment”
## How Big is the Problem?

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>&lt;65</td>
<td>2%</td>
</tr>
<tr>
<td>80</td>
<td>15%</td>
</tr>
<tr>
<td>90</td>
<td>40-50%</td>
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</tbody>
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- 35.6 million living with dementia
- 7.7 million new cases per year
- Projected to double every 20 years
- $604 billion worldwide

1:9 over 65 has AD
1:3 over 85 has AD
6\textsuperscript{th} leading cause of death in US
5.3 million currently affected
  - 500,000 new cases 2015 (65 sec)
  - 200,000 early onset
  - 2025: 7.1 million (40% increase)
  - 2050: 13.8 million (33 sec)
2014: 17.9b hrs of unpaid care from 15.7 million caregivers (80%)
  - Average caregiver: 22 hrs care/week
$226 billion direct billed costs
  - 44B out of pocket
  - 1.2 trillion in 2050
  - 500% increase in Medicare/caid
2/3 women
4-8 yr average survival, more time in severe stage than any other
## Not all Dementia is AD

<table>
<thead>
<tr>
<th>≤65yrs</th>
<th>Rapidly Progressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset AD</td>
<td>Creutzfeldt-Jakob</td>
</tr>
<tr>
<td>Frontotemporal lobar</td>
<td>Delirium</td>
</tr>
<tr>
<td>Degeneration (FTLD)</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>- Pick’s disease</td>
<td>- NMDA-receptor mediated encephalitis</td>
</tr>
<tr>
<td>- Primary Progressive</td>
<td>- Limbic encephalitis</td>
</tr>
<tr>
<td>Aphasia</td>
<td></td>
</tr>
<tr>
<td>- CBD</td>
<td></td>
</tr>
<tr>
<td>- PSP</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Infectious</td>
</tr>
<tr>
<td>- Limbic encephalitis</td>
<td>- Insect-borne illness</td>
</tr>
<tr>
<td></td>
<td>- Rabies</td>
</tr>
</tbody>
</table>
### Not all Dementia is AD

<table>
<thead>
<tr>
<th>Causes of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the above</td>
</tr>
<tr>
<td><strong>Vascular Disease</strong></td>
</tr>
<tr>
<td><strong>Lewy Body Disease</strong></td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Wernicke’s</td>
</tr>
<tr>
<td>Endocrine disturbances</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td>Toxic (Substance, heavy metals)</td>
</tr>
<tr>
<td>Adult leukodystrophies</td>
</tr>
<tr>
<td>Dementia Pugilistica/CTE</td>
</tr>
<tr>
<td>Polypharmacy</td>
</tr>
<tr>
<td>Parkinson’s Plus</td>
</tr>
<tr>
<td>Neurosyphilis</td>
</tr>
<tr>
<td>TB</td>
</tr>
<tr>
<td>Whipple’s</td>
</tr>
<tr>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Cerebral Amyloid Angiopathy</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Delayed Radiation encephalopathy</td>
</tr>
<tr>
<td>SLE/Sarcoidosis/autoimmune</td>
</tr>
</tbody>
</table>
Who, When, and How: Cognitive Screening
When should you screen?

- Annually > 65 yrs or if any red flags/concerns
- Medicare Annual Wellness Visit
Algorithm for Initial Evaluation

Yearly

Patient Eval
Physician, patient, informant

Concerns/red flags?

<table>
<thead>
<tr>
<th>Y</th>
<th>Concerns/red flags?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Cognitive Screen MMSE/3MS MoCA MIS GPCOG Mini-Cog</td>
</tr>
<tr>
<td>N</td>
<td>Screen</td>
</tr>
<tr>
<td>N</td>
<td>Reliable Informant Confirms?</td>
</tr>
<tr>
<td>Y</td>
<td>Follow-up Yearly or if concerns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Manage/Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Basic Work-up History Exam Labs Imaging</td>
</tr>
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</table>

Refer Neuropsychologic Eval Neurologist/Geri +/- Driving Eval
Concerns/Red Flags?

- If the physician, patient, or family member is concerned
- Age <65
- Non-memory complaints:
  - Falls
  - Balance problems
  - Depression
  - Changes in personality/behavior
  - Increase in driving errors
  - Delirium with medical illness
  - Trouble managing medications- missed doses, overdoses
  - History of head injury (repeated concussion, LOC, TBI)
  - REM Sleep Behavior Disorder
“no one tool is recognized as the best brief assessment to determine if a full dementia evaluation is needed”

For the Patient:
Mini-Cog™, the Memory Impairment Screen (MIS), and the General Practitioner Assessment of Cognition (GPCOG).
- relatively free of education, race or cultural bias
- take five minutes or less to administer
- Free

For the informant:
AD8, the Short Informant Questionnaire on Cognitive Decline in the Elderly (short IQCODE), and the Informant GPCOG.”
<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>Familiarity, Ease of use</td>
<td>Copyright, Insensitivity/Limited Variability</td>
</tr>
<tr>
<td>3MS</td>
<td>More graduated scoring, More domains tested than MMSE, More likely to pick up MCI</td>
<td>Requires some training</td>
</tr>
<tr>
<td>MoCA</td>
<td>Multiple versions, Tests more domains than MMSE, More likely to pick up MCI</td>
<td>10 minutes to administer, Requires training to do well, <a href="http://www.mocatest.org">www.mocatest.org</a></td>
</tr>
<tr>
<td>GPCOG</td>
<td>Free, Fast, Impaired triggers informant's</td>
<td>Inter-rater reliability (current events), <a href="http://www.alz.org/documents_custom/gpcog(english).pdf">http://www.alz.org/documents_custom/gpcog(english).pdf</a></td>
</tr>
</tbody>
</table>
What is part of **routine** primary care work-up?

**PLEASE DO**
- Complete blood cell count
- Serum electrolytes
- Glucose or HgbA1c
- Depression screening*

**PLEASE DON’T**
- RPR
- Genetic testing (ApoE, PSN, etc.)
- EEG
- Lumbar puncture
- Folate

- Thyroid function tests
- Liver function tests
- Serum B12 levels
Primary Care Work-up: Imaging

- MRI brain
  - No contrast necessary unless suspect space-occupying lesion/infection
    - Contrast if:
      - Atypical presentation (rate of decline, age, systemic symptoms like fever)
      - Lateralizing signs on neurologic exam
  - Specify dementia protocol to ensure correct imaging acquisition
  - Obtain prior imaging for comparison*
  - Make sure reading radiologist/neuroradiologist knows what you are looking for (temporal/parietal atrophy, white matter disease, hemosiderin, etc.)
  - Volumetric measurements rarely needed in primary care setting
Primary Care Work-up: Imaging

- CT head
  - Only if MRI brain is contraindicated
    - Pacemaker, cannot tolerate, etc.
- FDG-PET
  - Rare indication for ordering by PCP
  - Narrow indication for: FTD vs AD, known primary neoplasm (MRI may be more appropriate in these cases), paraneoplastic disease
- Amyloid PET
  - Almost never indicated, and not in primary care setting
Treatment: AD (+/- VCI)

- MCI: No current FDA-approved therapeutic
  - If amnestic MCI profile with evidence for progression: consider Chol-I
  - Off-label
  - No evidence to support
  - Risk of treating those who will stabilize
    - 12% all MCI progresses in 1 year
    - 15-25% of aMCI progresses/year
Cholinesterase Inhibitors

**General:**
- Indicated from mild dementia-severe dementia
- First line for behavioral management
- Watch for bradycardia, syncope, GI side effects
- Start at low dose and titrate to avoid side effects
- Modest effect: not disease modifying, may increase time to increased assistance
- Manage expectations!

Benefit still observed in mod/severe. Consider d/c when full care
Cholinesterase Inhibitors

- **Donepezil (Aricept):** ONLY Chol-I with indication in severe AD
  - Start at 5mg, titrate to 10mg nightly
  - 23mg: only for moderate to severe: higher incidence of side effects, $$$, minimal benefit, consider if significant language impairment

- **Rivastigmine (Exelon)**
  - PO: 1.5mg BID, 2 weeks later increase to 3mg BID (4.5/6)
  - patch- may require PO failure, start with 4.6mg/24hr, increase after 4 weeks
  - High dose recently FDA approved- not clear if any benefit over standard dose

- **Galantamine (Razadyne)**
  - 8/16mg
  - Benefit still observed in mod/severe. Consider d/c when full care
Memantine

Namenda

• Moderate-affinity non-competitive NMDA-R antagonist
• NOT indicated for mild dementia (MMSE>15 or independent in basic ADLs)
• Only use in mild dementia if fail Chol-I
• Titration pack: goal dose of 10mg BID or 28mgXR
• Generally well-tolerated, watch for
  • vivid dreams
  • worsening agitation
  • HA
  • Hallucinations
  • somnolence
Symptomatic Management

- Sleep
  - Avoid Benzos
  - Avoid anticholinergics/antihistamines
    - Incontinence, URI
- Behavior
  - Non-severe agitation: Chol-I and Memantine
  - Psychosis with/without agitation: atypical antipsychotics*
    - Acknowledge that it is not FDA-approved for this
    - Acknowledge black-box warning, discuss risk/benefit ratio
    - Pre-screen for prolonged QT
    - Lowest dose necessary for shortest time necessary
    - RE-EVALUATE FREQUENTLY
  - Agitation without psychosis: as above, antidepressants, mood stabilizers
Symptomatic Management

• **Depression**
  • Avoid MAO-I and tricyclics!
  • SSRI or SNRI, consider “activating” versus not

• **Apathy**
  • Distressing
  • No current approved treatments
  • Dopaminergic antidepressants (sertraline, buproprion), Chol-I, stimulants?, dopamine agonists
**Treatment: All Cognitive Impairment**

- **Exercise**: aim for increased heart rate, goal 120 min per week
- **Control vascular risk factors**, especially if evidence for contribution to cognitive decline
  - HLD, Diabetes, metabolic syndrome, smoking
  - Blood pressure**
- **Screen regularly and treat depression**
- **Address medical comorbidities**
- **Environmental Management**
  - Minimize overstimulation
  - Promote sleep and address parasomnias
  - Encourage social engagement
  - Minimize deviation from normal routines- plan ahead if needed
  - Caregiver support and respite
  - Screen regularly for safety, need for increased supervision, driving abilities
  - Evaluate for ID bracelets, wandering, etc.
Health maintenance is critical to avoid precipitous cognitive decline
  - Flu vaccines, pneumovax, routine physicals
Recognize potential need for alternative living arrangements
Consider appropriate therapies (speech, PT, OT)
Doc, should I take....?

- **Vitamin E**
  - No improvement in AD or MCI
  - Increased mortality at higher doses

- **Ginko Biloba**
  - Ginko Evaluation of Memory Study (3069 participants) did not find slowed cognitive decline

- **Coconut Oil**
  - Use on your skin, not in your food
  - Gastrointestinal distress
  - No proven cognitive benefit
  - Sugar versus Fat - let’s discuss

- **Caprylic acid (axona) and Ketasyn (no phase III)**

- **Huperzine- similar to Chol**

- **Tramiprosate (Vivimind)**
  - Phase III inconclusive, so marketed a medical food
On the horizon

Diagnosis and treatment
Advanced Imaging

• Not necessary if standard diagnostic criteria are met for single disorder

• **FDG-PET**
  • Currently only FDA-approved to distinguish frontotemporal degeneration from Alzheimer’s disease
  • $4000-8000, often not covered by private insurers
  • Technically sophisticated: operator variability
  • Would avoid if significant atrophy

• **Amyloid Imaging**
  • Concerns for high numbers of amyloid positive asymptomatic (30%)
  • Much better as a rule out than a rule in
  • FDA approved (single ligand), but not currently paid for
  • Useful in the context of clinical trials
  • Current recommendations: Not part of standard dementia work-up
  • Consider referral for IDEAS study if Medicare
• Unnecessary if clinical diagnosis is solid
• Significantly less expensive than standard PET rates ($2500)
• Unlikely to be covered by insurance
• Risk of ambiguous results
• If +, increases risk of progression from MCI and elevated in asymptomatic DIA patients

### CSF Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Consistent w/AD</th>
<th>Inconsistent w/AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-42</td>
<td>Low</td>
<td>Normal/High</td>
</tr>
<tr>
<td>Total Tau</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>P-Tau</td>
<td>&gt;60</td>
<td>≤60</td>
</tr>
<tr>
<td>ATI</td>
<td>&lt;1.0</td>
<td>&gt;1.0</td>
</tr>
</tbody>
</table>
• Consider if strong family history (broaden definition of this)
• Whenever possible, engage a genetic counselor
• Know what you are testing for
  • Early onset AD panel
  • ApoE genotype for risk determination: CAUTION
  • FTD (can often narrow to a particular mutation and decrease cost to pt)
  • Test patient when possible
Clinical Trials

- 2008: 172 failed drugs
- New focus on Amyloid clearance, early intervention
  - Is it too late once the patient is symptomatic?
- Recent high profile failures
  - Amyloid-targeting antibodies (bapineuzumab/solanezumab)
  - Gamma-secretase inhibitors (semagacestat/avagacestat)
  - Gingko
- Enrolling and on the horizon
  - Amyloid targeting
    - BACE-inhibitors (target cleavage of APP)
    - Ab, vaccines, ApoE targeting, Y-secretase inhibitors
  - Tau targeting
  - Selective 5-HT6 receptor antagonists
  - Nicotinic R agonists
  - Histamine antagonists
  - Mao-B
  - GABA R inhibitors
  - Inhaled insulin
Multi-Disciplinary Clinics

Reduce burden on patients and caregivers

- Neurologists
- Social Workers
- Alzheimer’s Association engagement
- Nurse practitioners
- Neuropsychologists
  - Initial evaluation
  - Feedback and interpretation
  - Interim brief testing
  - Psychosocial support
- Clinical Research Coordinators
- Case workers
- Genetic Counselors
- PT/OT/Speech Therapists
• **MACC**
  • Multi-D approach
  • 3 Neurologists
  • Scheduling within 4 weeks in most cases
    • (434) 924-8668
• **Clinical Trials**
  • 5 trials in process
    • Prodromal AD (amnestic MCI)
    • Pick’s Disease
    • Mild-moderate AD
  • Contact Colleen Webber
  • cmn6x@virginia.edu
  • (434)243-5898

• **Alzheimer’s Association**
  • Caregiver support
  • Patient services

• **AFTD**
  • theaftd.org

• **American Heart Association**
  • Diet/exercise recommendations
Selected References


