Treating Dementia:
A Course for Primary Care Physicians
Learning Objectives

- Describe prevalence and impact of dementia
- Describe diagnostic evaluation of Alzheimer’s disease and related dementias
- Review neuropathology of Alzheimer’s disease
- Describe treatment options
  - Pharmacologic and non-pharmacologic
- Identify risk management issues
- Discuss current research
2018 ALZHEIMER’S DISEASE FACTS AND FIGURES

ALZHEIMER’S DISEASE IS THE 6TH leading cause of death in the United States

16.1 MILLION AMERICANS provide unpaid care for people with Alzheimer’s or other dementias

These caregivers provided an estimated 18.4 BILLION HOURS of care valued at over $232 BILLION

Between 2000 and 2015 deaths from heart disease have decreased 11% while deaths from Alzheimer’s disease have increased 123%

1 IN 3 seniors dies with Alzheimer’s or another dementia

It kills more than breast cancer and prostate cancer COMBINED

EARLY AND ACCURATE DIAGNOSIS COULD SAVE UP TO $7.9 TRILLION in medical and care costs

IN 2018, Alzheimer’s and other dementias will cost the nation $277 BILLION

BY 2050, these costs could rise as high as $1.1 TRILLION

5.7 MILLION Americans are living with Alzheimer’s

BY 2050, this number is projected to rise to nearly 14 MILLION

EVERY 65 SECONDS someone in the United States develops the disease
Impact of Dementia on Utilization

Average Annual Per-Person Payments for Health Care Services Provided to Medicare Beneficiaries Age 65 and Older with and without Alzheimer’s Disease and Other Dementias, in 2014 Dollars

<table>
<thead>
<tr>
<th>Service</th>
<th>Beneficiaries with Alzheimer’s Disease and Other Dementias</th>
<th>Beneficiaries without Alzheimer’s Disease and Other Dementias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient hospital</td>
<td>$11,370</td>
<td>$4,571</td>
</tr>
<tr>
<td>Medical provider*</td>
<td>6,306</td>
<td>4,181</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>4,189</td>
<td>487</td>
</tr>
<tr>
<td>Nursing home</td>
<td>19,442</td>
<td>864</td>
</tr>
<tr>
<td>Hospice</td>
<td>1,925</td>
<td>188</td>
</tr>
<tr>
<td>Home health</td>
<td>1,543</td>
<td>498</td>
</tr>
<tr>
<td>Prescription medications**</td>
<td>2,889</td>
<td>2,945</td>
</tr>
</tbody>
</table>

Source: Alzheimer’s Disease Facts and Figures
Coexisting medical conditions among older adults with Alzheimer’s disease

77% of patients have ≥3 additional chronic conditions and 95% have at least one additional chronic condition

<table>
<thead>
<tr>
<th>Coexisting Condition</th>
<th>Percentage of People with Alzheimer’s Disease and Other Dementias Who Also Had Coexisting Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>30%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>22%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>17%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>17%</td>
</tr>
<tr>
<td>Stroke</td>
<td>14%</td>
</tr>
<tr>
<td>Cancer</td>
<td>9%</td>
</tr>
</tbody>
</table>

Source: Alzheimer’s Disease Facts and Figures and CMS data
Reasons for Hospitalization:
% of admission diagnosis

<table>
<thead>
<tr>
<th>Reason for Hospitalization</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, fall, trauma</td>
<td>26%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>17%</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>9%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6%</td>
</tr>
<tr>
<td>Delirium, mental status change</td>
<td>5%</td>
</tr>
</tbody>
</table>

*All hospitalizations for individuals with a clinical diagnosis of probable or possible Alzheimer’s disease were used to calculate percentages. The remaining 37 percent of hospitalizations were due to other reasons. Created from data from Rudolph et al. [2021]*

Source: Alzheimer’s Disease Facts and Figures
Adverse Health Events

- 3 to 6 times more likely to develop delirium
- 1.6 to 5 times more likely to fall
- 5 times more likely to develop new urinary incontinence
- 6 times more likely to develop fecal incontinence
- 5 times more likely to develop pressure sores
What Every Physician Should Know

- More than 80% of all medical care for dementia occurs in general medical setting
- You have tools to diagnose AD and other dementias!
- The HOPE Act: Medicare reimbursement for care planning (99483)
- Early identification is key for research and clinical outcomes
  - Only 50% with disease are diagnosed
  - 50% of those already in moderate disease stage
  - Disease modifying treatments have less impact
Dementia: Impairment in one or more cognitive domains that interferes with independence

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex attention</td>
<td>Ability to attend to and process multiple stimuli</td>
</tr>
<tr>
<td>Executive function</td>
<td>Ability to plan, organize, and complete tasks/projects</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Acquiring, manipulating, and remembering items, facts, words and their meanings, events, people, procedures, skills, etc.</td>
</tr>
<tr>
<td>Perceptual-motor</td>
<td>Identification and manipulation of figures, maps and items; motor tasks; recognition of faces and colors</td>
</tr>
<tr>
<td>Language</td>
<td>Expressive and receptive language skills</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Socially appropriate behaviors and decision-making; empathy</td>
</tr>
</tbody>
</table>
Diseases Causing Dementia

- Vascular Dementia
- Dementia with Lewy Bodies
- Parkinson’s Disease
- Frontotemporal Dementia
- Huntington’s Disease
- Creutzfeldt-Jakob Disease
- Normal Pressure Hydrocephalus (NPH)
- Traumatic Brain Injury
- Down Syndrome Dementia
- Korsakoff Syndrome

Alzheimer’s Disease
Potentially Reversible Causes of Cognitive Impairment

- **Depression**
  - Independent risk factor for Alzheimer’s disease
  - Distinguish depression from apathy
- **Medication Side Effects**
  - Opioids
  - Anti-cholinergics
  - Sedative hypnotics
- **Hypothyroidism**
- **Sleep disorders**
- **Vitamin Deficiencies, especially B12 and D**
- **Excessive alcohol use or substance abuse**
  - Underreported in elderly
Progression of Alzheimer’s Disease: similar model for other neurodegenerative diseases

Presymptomatic (AD At-Risk)

MCI (Likely due to AD)

Alzheimer’s Dementia

Accumulating pathology and brain dysfunction (biomarkers)

Disease Progression

Cognitive Function
Progression of Alzheimer’s Disease

May begin up to 20 years prior to Clinical

Preclinical AD
- No clinical signs of cognitive decline
- Underlying AD pathology (CSF or PET)
- May or may not progress to clinical AD

Prodromal AD
Also referred to as:
- Mild Cognitive Impairment (MCI)
- Amnestic MCI due to AD
- Symptomatic predementia of AD
- Minor change in cognition and short-term memory loss

Alzheimer’s Dementia
Full Clinical Dementia
- Memory loss
- Cognitive impairment
- Behavioral changes
- Motor and speech dysfunction, etc.
Biomarker Changes Begin Years before Symptoms Emerge (reflecting neuropathology)

Figure adapted from Jack et al. 2010
Sperling et al Alzheimer’s & Demential 2011
The Importance of Early Diagnosis and Disclosure

Leads to Better Outcome for Individuals and Caregivers

- Access Available Treatments
- Build Care Team
- Participate in Clinical Trials
- Access Support Services
- Better Manage Medications
- Receive Counseling
- Address Driving and Safety Issues
- Manage Co-Occurring Conditions
- Advance Planning

Early and Accurate Diagnosis Could Save Up to $7.9 Trillion in Medical and Care Costs
Diagnostic Challenges for the PCP

• Time for and access to standardized screening protocols

• Additional training specific to dementia care

• Concern about risk of misdiagnosis

• Concern about stigmatization of diagnosis

• Perception of limited treatment options

• Support resources
Making the Diagnosis in the General Care Setting

Initial Assessment
- History from patient and family member/close friend
- Relevant medical history and medication review
- Laboratory assessment if indicated
  - TSH, vitamin B12, homocysteine
  - CBC/Chem 20, ESR, CRP

Screening for Memory Loss
- Cognitive screen
- PMOCA: no royalties, simple
- MMSE
  - Available on the Alzheimer’s Toolkit App
- Psychiatric screen

Referral to a Specialist
- Imaging: used to rule out other causes
- Specialty referral: Neurology, geriatric psychiatry, neuropsychology
- Dependent on individual comfort level and experience
- PCP or family may desire specialized office-based assessment
- Consider MRI to evaluate for CVA or related pathologies
- Specialist tests may include: FDG PET, Amyloid PET, spinal fluid examination
Current Management Options
Pharmacological and Behavioral
Multiple Components of AD Management

Initial Evaluation
- Early detection
- Comprehensive history
- Physical exam + labs
- Mental status exam
- Neuroimaging
- Psychiatric assessment

Ongoing Management
- Medication review
- Treatment of cognitive symptoms
- Treatment of psychiatric symptoms
- Assessment of MS changes
- Proactive treatment of comorbidities

Patient

Medical Team

Support System

Caregiver
- Assessment for burden, depression
- Disease education
- Access to local resources
- Individual and group therapy
- Respite time

Psychosocial
- Adequate supervision
- Safety review
- Advance directives
- Financial planning
- Meaningful activities
- Physical exercise
- Healthy diet
- Social stimulation
Risks for Caregivers

• Dementia caregivers are at increased risk for:
  ▪ Social isolation
  ▪ Physical ill health
  ▪ Financial hardship
  ▪ Depression and stress

• Support/ education for the patient/ caregiver partnership is essential in dementia care

• Improving caregiver well being through interventions that provide counseling and support can relieve caregiver burden and delay nursing home admission.
## Pharmacological Interventions

### FDA-approved drugs

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name</th>
<th>Approved for</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>donepezil</td>
<td>Aricept</td>
<td>All stages</td>
<td>1996</td>
</tr>
<tr>
<td>galantamine</td>
<td>Razadyne</td>
<td>Mild to moderate</td>
<td>2001</td>
</tr>
<tr>
<td>memantine</td>
<td>Namenda</td>
<td>Moderate to severe</td>
<td>2003</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>Exelon</td>
<td>All stages</td>
<td>2000</td>
</tr>
<tr>
<td>donepezil and memantine</td>
<td>Namzaric</td>
<td>Moderate to severe</td>
<td>2014</td>
</tr>
</tbody>
</table>
Set Expectations: Some patients may experience clear benefit, but all decline within 6-12 months.


AChEI = acetylcholinesterase inhibitor

Diagram shows the mean change from baseline in ADAS-cog score over months for placebo and galantamine groups, with double-blind and open-extension phases.
Combination Therapy vs Monotherapy in AD dementia

The European Academy of Neurology Guidelines (2015) recommend combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD.²

This recommendation was based on pooled data from four long-term trials (N=1549) demonstrated significant benefits of this combination therapy vs. monotherapy.²

Addition of memantine XR to a stable dose of ChEI results in significant benefits in cognition and global functioning.³,⁴

MEM= memantine; ChEI= acetylcholinesterase inhibitor; IMC= Information-Memory-Concentration; BDS (Blessed Dementia Scale).

Changes in mood, perceptions, thought content or behavior in dementia are common, burdensome and costly to families and systems of care.

**BPSD include:** apathy, depression, agitation, sleep disturbance, irritability, anxiety, disinhibition, delusions, hallucinations.

BPSD may be due to dementia-related brain changes, co-morbid conditions (e.g. infection, pain, constipation) or may be responses to environmental conditions.
BPSD Management

- Treatment guidelines recommend non-pharmacological strategies as a first-line intervention:
  - Creating pleasurable or meaningful activities
  - Simplifying tasks
  - Enhancing communication

- Pharmacological treatments of agitation and psychosis in dementia include:
  - **Citalopram** 10-20 mg / **Escitalopram** 5-10 mg daily
  - **Risperidone*** 0.5-2 mg daily
  - **Aripiprazole*** 5-10 mg daily
  - **Quetiapine*** 25-200 mg daily
  - **Olanzapine*** 2.5 -10 mg daily

* Black box warning (increased mortality) and FDA warning (increased CVA risk) for all atypical antipsychotics
Lifestyle Interventions

• Healthy Nutrition (Mediterranean Diet, limited alcohol use)

• Exercise

• Social engagement

• Optimal sleep hygiene

• Intellectual Stimulation
Risk Management: Driving

- Early AD increases crash risk by as much as 7x
- Early AD increases risk of becoming lost while driving
- Cognitive screening (MMSE< 24; MOCA <18) – refer for road test
- Alzheimer’s shortens attention span; impairs visual-spatial ability, sequencing and cognitive mapping skills

Management Options

- Counsel patient and care partner about driving risks
- Physician reporting is voluntary in MA
  - advise patient to self-report serious impairment to RMV
  - for serious concerns, seek legal advice and consider reporting to RMV Medical Affairs Branch
- Consider referral to Alzheimer’s Association, and for private driver evaluation
- For guidance, refer to AMA Ethical Opinion E-2.24
- Leave decision to certified driving evaluator to avoid patient conflict
Risk Management: Competence

- Undue Influence / Elder Abuse
- Vulnerability to Coercion
- Finances
- Medication
- Decision Making
- Home Safety
  - Cooking
  - Firearms
Wandering and becoming lost is:

- Common (60%)
- Recurrent (75%)
- Life-threatening (if not found 40% mortality)
- Highly stressful for care partners
- medicalert.org/safereturn
Advanced Care Planning

- Living Will/Health Care Proxy
- Durable Power of Attorney
- Plan for changing care needs over course of disease
- Preferences for end-of-life care
- Care planning covered by HOPE Act
Summary

- Dementia in older adults is associated with significant mortality and morbidity as well as cost.

- Alzheimer's disease is the most common form of dementia characterized by synapse loss as well as deposition amyloid plaques and neurofibrillar tangles.

- Early identification is key for research and clinical outcomes as well as planning and caregiver support.
Resources and Options
Resources

- Alzheimer’s Association
  - Leading voluntary health organization in Alzheimer’s care, support, and research
  - Mission
    - Eliminate Alzheimer’s disease through research
    - Provide and enhance care for all affected
    - Reduce risk of dementia through promotion of brain health
  - Direct Referrals
  - 24/7 Helpline: 800-272-3900
  - www.alz.org

- *Improving Hospital Care for Persons with Dementia.* Nina M. Silverstein & Katie Maslow

- Hospice Care for Patients with Advanced Progressive Dementia. Ladislav Volicer and Ann Hurley

- *The Alzheimer’s Health Care Handbook,* Mary S. Mittleman, Dr. PH & Cynthia Ep

- *Alzheimer’s Association Facts & Figures*
Current Research
What’s next?
The New Generation of Treatment for Alzheimer’s Disease

- Aimed at underlying pathology
- Primarily amyloid based approaches
  - Decrease production of toxic form of amyloid
    - Secretase inhibitors
  - Decrease amyloid aggregation
  - Increase amyloid clearance – Immunotherapy
    - Vaccines
    - Antibodies
Drugs

- **Solanezumab**
  - Binds to β-amyloid, preventing formation of plaques

- **MK-8931**
  - Beta-secretase (BACE) inhibitor

- **AADvac1**
  - Attacks abnormal form of tau protein

- **CSP-1103**
  - Microglial modulator reduces inflammation

- **Intranasal insulin**
  - Increases insulin signaling in brain

- **Aducanumab**
Aducanumab Phase 1 Study
Results at 54 Weeks

Most common AEs with aducanumab were amyloid-related imaging abnormalities (ARIA), headache, urinary tract infection, and upper respiratory tract infection. Only serious AEs with aducanumab were ARIA (3–16% at 1–10 mg/kg) and CNS superficial siderosis.

**CDR-SB = Clinical Dementia Rating—Sum of Boxes; CNS = central nervous system.**

### RCTs in Presymptomatic AD

<table>
<thead>
<tr>
<th>RCT</th>
<th>ADCS-A4¹</th>
<th>API²</th>
<th>DIAN³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>Older adults without cognitive impairment (N = 1150)</td>
<td>Early onset familiar AD (Columbia +US) (N = 300)</td>
<td>Early-onset familial AD, no symptomatic or mild cognitive impairment (N = 240)</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Amyloid PET positive (control: negative)</td>
<td>Carrier <em>PSEN1</em> (control: non carrier)</td>
<td>Carrier of <em>PSEN1, PSEN2, APP</em> (N = 120) (control: non carriers)</td>
</tr>
<tr>
<td><strong>Age at enrollment</strong></td>
<td>65–85 years</td>
<td>30–60 years</td>
<td>18–80 years</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>solanezumab</td>
<td>crenezumab</td>
<td>gantenerumab and solanezumab</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>3 years + 2-year extension</td>
<td>5 years</td>
<td>2 years + 3 years extension</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary: cognitive function Secondary: change in AD biomarkers</td>
<td>Primary: cognitive function Secondary: change in AD biomarkers</td>
<td>Primary: cognitive function Secondary: qualification of algorithm based on <em>TOMM40</em> and <em>APOE</em></td>
</tr>
</tbody>
</table>

**RCT** = randomized controlled trial.

$100 million clinical trial backed by Alzheimer’s Association and funded largely by Medicare

Recruited more than 18,000 patients, 200 sites throughout the United States

Specific Aims
  • Assess impact of amyloid PET on patient management at 90 days
  • Assess the impact of amyloid PET on hospital admissions and emergency room visits at 12 months

Hopes to prove that doctors and families make different decisions when they know what they’re dealing with

Hoping scans will lead to fewer hospitalizations as the new diagnoses make families more vigilant

Could also lay the groundwork for how insurers will cover imaging for Alzheimer’s patients
Resources for Keeping Up with Current Trials

- FDA.gov
- ClinicalTrials.gov