DEMENTIA
OBJECTIVES

Know and understand:

• The risks for and causes of dementia
• Evaluation of patients with dementia
• How to plan behavioral and pharmacologic treatment strategies to minimize the personal, social, & financial impacts
• How to refer patients and caregivers to available community resources
TOPICS COVERED

• Demography and societal impact
• Risk factors and protective factors
• Diagnosis, including differential
• Treatment and management
• Resources
• Case study
Incidence of AD

1990: 4 Million American
       15 Million Worldwide

2050: 14 Million Americans
       36.7 Million Worldwide
       (25% of worldwide pop > 65)

Katzman et al, Epidemiology of AD, 1999
Janus, CNS Drugs 2003,457-474.
# Frequency of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Age Group</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69 yrs</td>
<td>1-2 %</td>
</tr>
<tr>
<td>70-74 yrs</td>
<td>4-5 %</td>
</tr>
<tr>
<td>75-79 yrs</td>
<td>7-10 %</td>
</tr>
<tr>
<td>80-84 yrs</td>
<td>15 - 20 %</td>
</tr>
<tr>
<td>over 85 yrs</td>
<td>40 + %</td>
</tr>
</tbody>
</table>

*Life Expectancy 8 – 10 years after symptoms begin*
Frequency of Alzheimer’s Disease

1 in 100 in those over 65 years of age

1 in 10 in those over 75 years of age

1 in 2-3 in those over 85 years of age

JL Cummings, 1997
WHAT IS DEMENTIA?

• An acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient
• Progressive and disabling
• NOT an inherent aspect of aging
• Different from normal cognitive lapses
NORMAL LAPSES vs DEMENTIA
Examples (1 of 2)

- Forgetting a name
- Leaving kettle on
- Finding right word
- Forgetting date or day
- Not recognizing family member
- Forgetting to serve meal just prepared
- Substituting inappropriate words
- Getting lost in own neighborhood
NORMAL LAPSES vs DEMENTIA
Examples (2 of 2)

Trouble balancing checkbook
Losing keys, glasses
Getting blues in sad situations
Gradual changes with aging

Not recognizing numbers
Putting iron in freezer
Rapid mood swings for no reason
Sudden, dramatic personality change
THE IMPACT OF DEMENTIA

Economic
• $199 billion annually for care and lost productivity
• Medicare, Medicaid, private insurance provide only partial coverage
• Families bear greatest burden of expense

Emotional
• Direct toll on patients
• Nearly half of caregivers suffer depression
RISK FACTORS FOR DEMENTIA

• Age
• Family history
• Head injury
• Fewer years of education
THE GENETICS OF DEMENTIA

Mutations of chromosomes 1, 14, 21
- Rare early-onset (before age 60) familial forms of dementia
- Down syndrome

Apolipoprotein E4 on chromosome 19
- Late-onset AD
- APOE*4 allele \( \uparrow \) risk & \( \downarrow \) onset age in dose-related fashion
- APOE*2 allele may have protective effect
PROTECTIVE FACTORS UNDER STUDY

• Estrogen replacement therapy after menopause

• NSAIDs

• Antioxidants
DIFFERENTIAL DIAGNOSIS FOR DEMENTIA

- Alzheimer’s disease
- Vascular (multi-infarct) dementia
- Dementia associated with Lewy bodies
- Delirium
- Depression
- Other (alcohol, Parkinson's disease [PD], Pick’s disease, frontal lobe dementia, neurosyphilis)
Alzheimer’s Disease is caused by Chlamydia Pneumoniae.

TRUE or FALSE

Brian Balin, PhD, PCOM
SYMPTOMS & SIGNS OF AD

- Memory impairment
- Gradual onset, progressive cognitive decline
- Behavior and mood changes
- Difficulty learning, retaining new information
- Aphasia, apraxia, disorientation, visuospatial dysfunction
- Impaired executive function, judgment
- Delusions, hallucinations, aggression, wandering
DSM-IV DIAGNOSTIC CRITERIA FOR AD

• Development of cognitive deficits manifested by both
  — impaired memory
  — aphasia, apraxia, agnosia, disturbed executive function

• Significantly impaired social, occupational function

• Gradual onset, continuing decline

• Not due to CNS or other physical conditions (e.g., PD, delirium)

• Not due to an Axis I disorder (e.g., schizophrenia)
PROGRESSION OF AD (1 of 3)

Mild Impairment

- Disorientation for date
- Naming difficulties
- Recent recall problems
- Mild difficulty copying figures
- Decreased insight
- Social withdrawal
- Irritability
- Mood change
- Problems managing finances
PROGRESSION OF AD (2 of 3)

Moderate Impairment

- Disorientation for date and place
- Comprehension difficulties
- Impaired new learning, calculating skills
- Getting lost in familiar areas, wandering
- Not cooking, shopping, banking
- Delusions, hallucinations
- Agitation, restlessness, anxiety, aggression
- Depression
- Problems with dressing and grooming
- Aphasia and apraxia
PROGRESSION OF AD (3 of 3)

Severe Impairment

- Nearly unintelligible verbal output
- Remote memory gone
- Unable to copy or write
- No longer grooming or dressing
- Incontinent
DSM-IV DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

- Development of cognitive deficits manifested by both
  - impaired memory
  - aphasia, apraxia, agnosia, disturbed executive function
- Significantly impaired social, occupational function
- Focal neurologic symptoms & signs or evidence of cerebrovascular disease
- Deficits occur in absence of delirium
DEMENTIA ASSOCIATED WITH LEWY BODIES

• Dementia

• Visual hallucinations

• Parkinsonian signs

• Alterations of alertness or attention
Delirium and dementia often occur together in older hospitalized patients; the distinguishing signs of delirium are:

- Acute onset
- Cognitive fluctuations over hours or days
- Impaired consciousness and attention
- Altered sleep cycles
DEPRESSION vs DEMENTIA

The symptoms of depression and dementia often overlap; patients with primary depression:

• Demonstrate ↓ motivation during cognitive testing

• Express cognitive complaints that exceed measured deficits

• Maintain language and motor skills
Cognitive Screening Instruments
AAN - Good Evidence

MMSE – adjusted for age/education- also affected by ethnicity
  • Sensitivity 71-92%
  • Specificity 56-96%

Memory Impairment Screen
Neuropsychological batteries

NEUROLOGY 56 May(1 of 2), 2001
AAN Guidelines
Mental Status Exam

I. Quantitative testing is necessary:
   A. Mini-mental (MMSE): good screen*
      1. 26-30: ok (consider prior IQ)
      2. 20-26: mild deficit
      3. 10-20: moderate deficit
      4. < 10: severe

*AAN Guidelines, 2001
B. Neuropsychiatric tests*
C. ADAS-Cog: 1-70 (Alzheimer’s Disease Assessment Cognitive Scale)
D. CIBIC-Plus: 1-7 (Clinician’s Interview Based Impression of Change plus caregiver input scale)
E. Clinical dementia rating (CDR): 0, 0.5, 1, 2, 3

*AAN Guidelines, 2001
USPSTF Recommendations

Evidence is insufficient to recommend for or against routine screening for dementia in older adults – NO randomized trials available

Some screening tests have good sensitivity but only fair specificity in detecting cognitive impairment and dementia

Could not determine whether the benefits of screening for dementia outweigh the harms
ASSESSMENT: HISTORY (1 of 4)

Ask both the patient & a reliable informant about the patient’s:

• Current condition
• Medical history
• Current medications & medication history
• Patterns of alcohol use or abuse
• Living arrangements
ASSESSMENT: PHYSICAL (2 of 4)

Examine:
- Neurologic status
- Mental status
- Functional status

Include:
- Quantified screens for cognition
  - e.g., Folstein’s MMSE, Mini-Cog
  - Neuropsychologic testing
Laboratory tests should include:

- Complete blood cell count
- Blood chemistries
- Liver function tests
- Serologic tests for: Syphilis, TSH, Vitamin $B_{12}$ level
Use imaging when:

- Onset occurs at age < 65 years
- Symptoms have occurred for < 2 years
- Neurologic signs are asymmetric
- Clinical picture suggests normal-pressure hydrocephalus

Consider:

- Noncontrast computed topography head scan
- Magnetic resonance imaging
- Positron emission tomography
AAN Guideline Summary

Diagnosis of Dementia

- Use clinical criteria: NINCDS-ADRDA & DSM-IV
- Diagnostic criteria imperfect for VD, Lewy body & Fronto-temporal dementia
- Structural neuroimaging appropriate
- CSF-14-3-3 protein – Useful in CJD

NEUROLOGY 56( May 1 of 2), 2001
Routine Evaluation parameters:

- CBC
- Serum lytes
- Gluc-BUN/creat
- Serum B12
- Liver function tests
- Thyroid function tests
- Depression screening
AAN Guideline Summary

NOT included in routine evaluation:

- Syphilis screening
- Linear/Volumetric MR or CT
- SPECT
- Genetic testing for DLB/CJD
- APOE genotyping for AD
- EEG
- Lumbar Puncture
AAN Guideline Summary

Can’t Support/Refute the following:

- PET
- Genetic markers for AD (not mentioned)
- CSF/Biomarkers for AD (Tau mutations in FTD)
- AD gene mutations in FTD

NEUROLOGY 56 may (1 of 2), 2001
TREATMENT & MANAGEMENT

Primary goals: to enhance quality of life & maximize functional performance by improving cognition, mood, and behavior

• Nonpharmacologic

• Pharmacologic

• Specific symptom management

• Resources
NONPHARMACOLOGIC

• Cognitive enhancement
• Individual and group therapy
• Regular appointments
• Communication with family, caregivers
• Environmental modification
• Attention to safety
PHARMACOLOGIC

• Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
• Other cognitive enhancers: estrogen, NSAIDs, ginkgo biloba, vitamin E
• Antidepressants
• Antipsychotics
Dementia Management

- Treat cognitive sx of AD with Cholinesterase Inhibitors and Vitamin E

NEUROLOGY May (1 of 2), 2001
Acetylcholinesterase Inhibitors

Effects on Cognitive Symptoms

- Those on placebo never catch up to those on active tx
- Less decline on ADAS-cog

NEUROLOGY May (1 of 2), 2001
USPSTF Recommendations

Fair to good evidence that several drug therapies have a beneficial effect on cognitive function (equivalent to delaying the natural progression of AD from 2-7 mths)

Evidence of beneficial effects on IADL’s is mixed, with the benefit being small at best
### Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Selectivity</th>
<th>Max serum conc</th>
<th>Food Delays Absorption</th>
<th>Serum Half-Life</th>
<th>Protein Binding (%)</th>
<th>Dose (mg/day)</th>
<th>Daily Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine (Cognex)</td>
<td>Btrle &gt; ACHE</td>
<td>1-2 hrs</td>
<td>Yes</td>
<td>1.3-2 hrs</td>
<td>75</td>
<td>80-160</td>
<td>4</td>
</tr>
<tr>
<td>Donepezil (Aricept)</td>
<td>ACHE</td>
<td>3-5 hrs</td>
<td>No</td>
<td>70-80 hrs</td>
<td>96</td>
<td>5-10</td>
<td>1</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>ACHE = Btrle</td>
<td>.5-2 hrs</td>
<td>Yes</td>
<td>2 hrs</td>
<td>40</td>
<td>6-12</td>
<td>2</td>
</tr>
<tr>
<td>Galantamine (Reminyl)</td>
<td>ACHE; Nic Mod</td>
<td>30-60 min</td>
<td>Yes</td>
<td>5-7 hrs</td>
<td>10-20</td>
<td>16-24</td>
<td>2</td>
</tr>
</tbody>
</table>
## Trials for AChE Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose (mg/D)</th>
<th>ADAS cog $\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine</td>
<td>80 – 160</td>
<td>2.2</td>
</tr>
<tr>
<td>Donepezil</td>
<td>5 – 10</td>
<td>2.9</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>6 – 12</td>
<td>3.8</td>
</tr>
<tr>
<td>Metrifonate</td>
<td>30 – 60</td>
<td>2.9</td>
</tr>
<tr>
<td>Galantamine</td>
<td>16 – 24</td>
<td>3.9</td>
</tr>
</tbody>
</table>

ADAS – cog 0 – 70; Decline 6 – 12 /yr
### Cholinesterase Inhibitors: Side Effects

#### Treatment-emergent side effects expressed as Drug % minus placebo % occurrence.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Donepezil 5mg</th>
<th>Donepezil 10mg</th>
<th>Rivastigmine 1-4mg</th>
<th>Rivastigmine 6-12mg</th>
<th>Galantamine 24mg</th>
<th>Galantamine 32mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td>37</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>24</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>17</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

** Raskind MA, et al. Neurology;54:2261-2268  

Not based on head to head comparisons
Acetylcholinesterase Inhibitors

Effects on Functional Symptoms

• Slows functional decline (ability to perform ADL’s and IADL’s)
Activities of Daily Living Scales

Summary Effect

Forrette, 1999
Imbimbo, 1998
Cummings, 1998
Agid, 1998
Zemlan, 1996
Thal, 1996
Rogers & Friedhoff, 1996
Forette, 1995
Antuono, 1995
Knapp, 1994
Davis, 1992
Molloy, 1991
Eagger, 1991
Thal, 1989

Instrumental Activities of Daily Living Scales

Favors

Cholinesterase Inhibitor

Favors Placebo

(-1.04)

Donepezil - Nursing Facility Placement

Delay of almost 2 years in time to first dementia-related nursing facility placement

Minimal donepezil exposure associated with shortest median time to nursing facility placement

Length of treatment appears to correlate with length of delay in nursing facility placement

Rationale for Considering Changing/Discontinuation of Cholinesterase Inhibitors

D/C may result in declining
Do not switch a patient who is benefiting from current medication

Why switch?
• Intolerable side effects
• Accelerated worsening
• Compliance/Cost
Acetylcholinesterase Inhibition Summary

- Stabilize cognitive decline
- Stabilize functional decline
- Stabilize behavior
- Improvement can occur
- May decrease caregiver burden
- May delay institutionalization
- Don’t cure
NMDA-receptor Antagonists
N-methyl-D-aspartate

Glutamate involved with learning and memory (principal excitatory neurotransmitter)
In AD, excessive glutamate production
Result is glutamate excitotoxicity (neuronal damage)
Blocking NMDA receptor- prevent neural cell death
Memantine

NMDA receptor antagonist – blocker of glutamate gated NMDA receptor channels
Modulates glutamate

European studies:

- Moderate severe to severe Alzheimer’s Disease
- Initiates functional improvement
- Caregiver noted cognitive and motor functions
- Minimal side effects

Pharmacopsychiatry 2000; 33(3): 103-8
Int. J. Geriatr Psychiatry 1999; 14: 135-146.
Memantine

Begin 5mg daily and increase by 5mg/week
From 4th week on can maintain 20 mg/day
Renal impairment- cr cl < 60 ml/min
  • ↓ 10 mg/day
Avoid amantadine, ketamine, dextromethorphan
Axura/ Ebixa/ Nemanda
NMDA Receptor Antagonists
Memantine

- MMSE 3 – 14, GDS 5 or 6, FAST 6a
- 28 wk, double-blind, parallel group study
- 252 subjects – mean age 76
- Memantine 20 mg/day vs. placebo
- Efficacy: CBIC-Plus, ADCS-ADLsev, MMSE, Severe Impairment Battery, GDS, FAST, Resource Utilization in Dementia
- CONCL: reduced clinical deterioration in mod to severe AD

NEJM 348:14 April 3, 2003
NMDA Receptor Antagonists
Memantine

Mild to Moderate Vascular Dementia
Multicenter 28 wk placebo controlled trial
288 subjects
MMSE 12-20
Results:
  ADAS-cog $\Delta$ 2 pts
  MMSE $\Delta$ 1.7
  CGI-C Improved/Stabilized

Memantine Tx in Pts with Mod to Severe AD already receiving Donepezil

Randomized, double-blind, placebo controlled trial

404 patients with mod to severe AD (MMSE 5-14) (322 pts completed)

Measures: Severe Impairment Battery, modified 19 item AD Cooperative Study ADL Inventory, CIBIC-Plus, NPI

JAMA, Jan 21,2004, Vol 291,No 3
Memantine Tx in Pts with Mod to Severe AD already receiving Donepezil

Memantine + Donepezil

- More completed study in combo group (172/150; p=.01)
- Improved cognition, ADL’s, global outcome, behavior
- Less agitation, diarrhea, fecal incontinence
- More headache and mild confusion
- Concl: Combo well tolerated

JAMA, Jan 21, 2004; Vol 291, No 3
Ginkgo Biloba

Extract of leaves of maidenhair tree
Probably originated in China
Oldest living tree species
Survives 1000 yrs
Marketed as food supplement in USA
Actions: ↑ blood supply by dilation, ↓ blood viscosity, modification of neurotransmitters, ↓ free radicals, inh. Platelet-activating factor
Inconsistent results in trials (ADAS-cog 1.5 ∆)
Compounds Under Investigation for AD

Vaccines
Statins
Anti-inflammatory agents
Metal Chelators
Secretases
CNS Neurotrophic Factors
Homocysteine Reducers
SYMPTOM MANAGEMENT

• Sundowning
• Psychoses (delusions, hallucinations)
• Sleep disturbances
• Aggression, agitation
• Hypersexuality
TO REDUCE SUNDOWNING (1 of 2)

• Provide orientation clues
• Give adequate daytime stimulation
• Evaluate for delirium
• Maintain adequate levels of light in daytime
• Establish bedtime routine and ritual
• Provide consistent caregivers
• Remove environmental factors that might keep patient awake
• Discourage drinking stimulants or smoking near bedtime
TO REDUCE SUNDOWNING (2 of 2)

- Give diuretics, laxatives early in day
- Provide personal care at same time each day
- Ensure patient has glasses, working hearing aid
- Place familiar objects at bedside
- Monitor amount of sensory stimulation
- Consider late afternoon bright light exposure
- Avoid prn sedative hypnotics
- Establish regular dose of drug for disturbing behavior (if needed)
- Assist caregiver in obtaining respite help
Antipsychotic medications (side effects):

- Higher potency: haloperidol (extrapyramidal symptoms)
- Lower potency: thioridazine (anticholinergic effects, sedation, hypotension, constipation, urine retention)
- Atypical antipsychotics: clozapine, risperidone, olanzapine

*(see next slide for dosing)*
# ANTIPSYCHOTICS TO USE CAUTIOUSLY IN OLDER DEMENTED PATIENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Peak Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>12.5-25 mg twice daily</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.25 at bedtime</td>
<td>3-5 mg daily</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.25-2.5 mg at bedtime</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25-0.5 mg at bedtime</td>
<td>1-1.5 mg daily</td>
</tr>
</tbody>
</table>

Note: Start low, go slow.
MANAGING SLEEP DISTURBANCES

- Improve sleep hygiene (e.g., consistent bedtime, comfortable setting)
- Provide daytime activity, prevent daytime sleeping
- Use bright-light therapy
- Treat associated depression, delusions
- If the above do not succeed, consider:
  - trazodone 25-150 mg
  - nefazodone 100-500 mg
  - zolpidem 5-10 mg
- Avoid benzodiazepines or antihistamines
MANAGING AGGRESSION AND AGITATION

• Behavioral interventions: distraction, supervision, routine, structure

• Behavior modification using rewards

• Pharmacologic interventions: antipsychotics, antidepressants, mood stabilizers, buspirone, β-blockers

• Avoid physical restraints
MANAGING HYPERSEXUALITY

• Treat underlying syndrome, such as mania

• Consider antiandrogens for men who are dangerously hypersexual or aggressive:
  — Progesterone 5 mg po daily; adjust dose to suppress testosterone well below normal
  — If responsive, may treat with 10 mg IM depot progesterone weekly
  — Leuprolide acetate 5-10 mg IM monthly is an alternative
RESOURCES FOR MANAGING DEMENTIA
(1 of 2)

• Specialist referral to:
  — geriatric psychiatrist
  — neurologist
  — neuropsychologist

• Social worker

• Physical therapist

• Nurse
RESOURCES FOR MANAGING DEMENTIA
(2 of 2)

- Attorney for will, conservatorship, estate planning

- Community: neighbors & friends, aging & mental health networks, adult day care, respite care, home-health agency

- Organizations: Alzheimer’s Association, Area Agencies on Aging, Councils on Aging

- Services: Meals-on-Wheels, senior citizen centers
SUMMARY (1 of 2)

- Dementia is common in older adults but is NOT an inherent part of aging

- AD is the most common type of dementia, followed by vascular dementia and dementia with Lewy bodies

- Evaluation includes history with informant, physical & functional assessment, focused labs, & possibly brain imaging
SUMMARY (2 of 2)

• Primary treatment goals: enhance quality of life, maximize function by improving cognition, mood, behavior

• Treatment may use both medications and nonpharmacologic interventions

• Community resources should be used to support patient, family, caregivers
CASE #1 (1 of 3)

An 83 y.o. nursing-home resident with moderately severe AD has had intermittent delusional thoughts and anxiety, but these have not been prolonged. He has had mild chronic renal failure, anemia, and a fractured hip but now ambulates well. He takes no psychotropic medications and sleeps well.

During the past 2 weeks, however, he has spent increasing amounts of time wandering the halls. He has also entered another patient’s room and rummaged through belongings and once was found outside the building.
CASE #1 (2 of 3)

Which of the following is the most appropriate treatment strategy?

(A) Provide structured physical activity and accompanied outdoor walks

(B) Use a vest restraint in a chair intermittently during the day

(C) Use wrist restraints during episodes of particularly vigorous walking

(D) Prescribe risperidone 1 mg po bid

(E) Transfer the patient to another nursing home
CASE #1 (3 of 3)

Which of the following is the most appropriate treatment strategy?

(A) Provide structured physical activity and accompanied outdoor walks

(B) Use a vest restraint in a chair intermittently during the day

(C) Use wrist restraints during episodes of particularly vigorous walking

(D) Prescribe risperidone 1 mg po bid

(E) Transfer the patient to another nursing home
ACKNOWLEDGMENTS

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