An 80-year-old woman is brought to the office because she has hallucinations of children and small animals when she is alone in a room. The hallucinations sometimes disturb and agitate her.

Her family also notes that she is having more difficulty walking and has hand tremors when she sits quietly.

She has a 9-month history of short-term memory loss; problems with orientation that sometimes worsen dramatically; and difficulty managing her finances, preparing complex meals, and following TV shows.
Her score on the Mini–Mental State Examination is 23 of 30.

On physical examination, there are signs of cogwheel rigidity and resting tremors, which have been noted for the past year.
Which of the following is the most likely diagnosis?

A. Dementia with Lewy bodies
B. Alzheimer disease
C. Parkinson disease with dementia
D. Huntington disease
Which of the following is the most likely diagnosis?

A. Dementia with Lewy bodies
B. Alzheimer disease
C. Parkinson disease with dementia
D. Huntington disease
A 67-year-old man comes to the office to establish care.

History includes mild hypertension.

The patient is married and maintains an active professional and social life. He is physically active, does not smoke, and drinks 1–2 glasses of wine daily.

Medications include hydrochlorothiazide 12.5 mg/day, aspirin 81 mg/day, and a daily multivitamin.
• Family history is notable for an 84-year-old maternal aunt who recently died after 6 years in the memory-disorders unit of a nursing home.

• His aunt’s death has caused the patient to worry about his own risk of dementia. He requests a referral for genetic testing for Alzheimer disease.

• Physical examination is unremarkable.
CASE 2 (3 of 4)

Which of the following is true about risk of Alzheimer disease?

A. Mutations in 4 known deterministic (causative) genes are associated with autosomal-dominant AD.

B. The lifetime risk of developing AD in the general population is approximately 20%, assuming a life span of 75 to 80 years.

C. AD is sporadic in approximately 75% of all cases.

D. Genetic risk for AD varies by race and ethnicity.
Which of the following is true about risk of Alzheimer disease?

A. Mutations in 4 known deterministic (causative) genes are associated with autosomal-dominant AD.

B. The lifetime risk of developing AD in the general population is approximately 20%, assuming a life span of 75 to 80 years.

C. AD is sporadic in approximately 75% of all cases.

D. Genetic risk for AD varies by race and ethnicity.
OBJECTIVES

Know and understand:

• The risks for and causes of dementia

• The evaluation of patients with dementia

• How to plan behavioral and pharmacologic treatment strategies to minimize the personal, social, & financial impacts of dementia

• How to refer patients and caregivers to available community resources
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
The Epidemiology of Dementia

- 6%-8% of people ≥65 yr have Alzheimer dementia (AD)
  - Prevalence doubles every 5 yr
  - Nearly 45% of those aged 85+ have AD

- Vascular dementia co-occurs with an estimated 15%-20% of AD cases — “mixed dementia”

- Lewy body dementia (LBD) — second most common cause of dementia
THE IMPACT OF DEMENTIA

Economic
• $604 billion annually for direct costs of medical and social care and informal care
• Medicare, Medicaid, private insurance provide much of the direct costs — remaining costs with families and/or caregivers ($202.6 billion)

Emotional
• Direct toll on patients
• Nearly half of caregivers suffer psychological distress, especially depression
ETIOLOGY

- Alzheimer disease
  - Amyloid plaques/oligomers
  - Tau neurofibrillary tangles
- Lewy body and Parkinson dementia
  - Cytoplasmic α-synuclein inclusion bodies
- Frontotemporal dementia
  - Tau or ubiquitin proteins
RISK FACTORS FOR DEMENTIA

Protective Factors

*Definite:* unknown

*Possible*

- NSAIDs
- Antioxidants
- Intellectual activity
- Physical activity
- Statin

Risk Factors

*Definite*

- Age
- Family history
- APOE4 allele
- Down syndrome

*Possible*

- Head trauma
- Fewer years of formal education
- Late-onset major depressive disorder
- Cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, obesity)
ASSESSMENT: HISTORY

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

- Date of onset of current condition and nature of symptoms
- Medical history
- Current medications & medication history
- Patterns of alcohol use or abuse
- Living arrangements
ASSESSMENT: PHYSICAL

Examine:
- Neurologic status
- Mental status
- Functional status

Include:
- Quantified screens for cognition
  - For example, Folstein’s MMSE, Mini-Cog, SLUMS, MoCA
- Neuropsychologic testing
<table>
<thead>
<tr>
<th>Name</th>
<th>Items/ Scoring</th>
<th>Domains assessed</th>
<th>Web link (accessed Oct 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cog</td>
<td>2 items Score = 5</td>
<td>Visuospatial, executive function, recall</td>
<td><a href="http://geriatrics.uthscsa.edu/tools/MINICog.pdf">http://geriatrics.uthscsa.edu/tools/MINICog.pdf</a></td>
</tr>
<tr>
<td>SLUMS</td>
<td>11 items Score = 30</td>
<td>Orientation, recall, calculation, naming, attention, executive function</td>
<td><a href="http://medschool.slu.edu/agsuccessfully/pdfsurveys/slumsexam_05.pdf">http://medschool.slu.edu/agsuccessfully/pdfsurveys/slumsexam_05.pdf</a></td>
</tr>
<tr>
<td>MoCA</td>
<td>12 items Score = 30</td>
<td>Orientation, recall, attention, naming, repetition, verbal fluency, abstraction, executive function, visuospatial</td>
<td><a href="http://www.mocatest.org">www.mocatest.org</a></td>
</tr>
<tr>
<td>Folstein MMSE</td>
<td>19 items Score = 30</td>
<td>Orientation, registration, attention, recall, naming, repetition, 3-step command, language, visuospatial</td>
<td>For purchase: <a href="http://www.minimental.com">www.minimental.com</a></td>
</tr>
</tbody>
</table>
ASSESSMENT: LABORATORY

Routine
- CBC
- Na+
- BUN/Cr
- Fasting glucose
- RPR
- TSH
- Vitamin $B_{12}$ level

Optional (based on clinical exam and suspicion)
- Liver function
- Folic acid
- Homocysteine/methylmalonic acid
- Urinalysis / Toxicology
- CSF analysis
- HIV testing
Consider imaging when:

- Onset occurs at age <65 years
- Neurologic signs are asymmetric or focal
- Clinical picture suggests normal-pressure hydrocephalus
- Patient has had recent fall or other head trauma

Consider:

- Noncontrast computed topography head scan
- Magnetic resonance imaging
- Positron emission tomography
DIFFERENTIAL DIAGNOSIS

- Normal aging
- Mild cognitive impairment
- Delirium
- Depression
- Alzheimer disease
- Vascular dementia
- Lewy body dementia
- Other (frontotemporal dementia, alcohol, Parkinson disease, neurosyphilis)
NORMAL AGING

• No consistent, progressive deviations on testing of memory

• Some decline in processing and recall of new information: slower, harder

• Reminders work—visual tips, notes

• Absence of significant effects on ADLs or IADLs due to cognition
MILD COGNITIVE IMPAIRMENT

• Subjective complaint of decline in at least one cognitive domain: noticeable and measurable

• No impairment in independent living

• 9.4 to 14.3/1000 person-years convert to Alzheimer disease

• ~50% with amnestic MCI maintain stable level of impairment or return to normal cognitive status in 3–5 yr
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

Search for underlying dementia once delirium cleared.
The symptoms of depression and dementia often overlap:

- Impaired concentration
- Lack of motivation, loss of interest, apathy
- Psychomotor retardation
- Sleep disturbance
Patients with primary depression are generally unlike those with dementia in that they:

- Demonstrate ↓ motivation during cognitive testing
- Express cognitive complaints that exceed measured deficits
- Maintain language and motor skills

~50% presenting with reversible dementia and depression progress to dementia within 5 yr
ALZHEIMER DISEASE

• Onset: gradual

• **Cognitive symptoms:** memory impairment core feature with difficulty learning new information

• **Motor symptoms:** rare early, apraxia later

• **Progression:** gradual, over 8–10 yr on average

• **Lab tests:** normal

• **Imaging:** possible global atrophy, small hippocampal volumes
VASCULAR DEMENTIA

- **Onset:** may be sudden/stepwise
- **Cognitive symptoms:** depend on anatomy of ischemia, but dysexecutive syndrome common
- **Motor symptoms:** correlates with ischemia
- **Progression:** stepwise with further ischemia
- **Lab tests:** normal
- **Imaging:** cortical or subcortical changes on MRI
LEWY BODY DEMENTIA

- **Onset**: gradual
- **Cognitive symptoms**: memory, visuospatial, hallucinations, fluctuations
- **Motor symptoms**: parkinsonism
- **Progression**: gradual, but usually faster than AD
- **Lab tests**: normal
- **Imaging**: possible global atrophy
FRONTOTEMPORAL DEMENTIA

- **Onset:** gradual, usually age <60
- **Cognitive symptoms:** executive, language, and behavioral dysfunction, including disinhibition and hyperorality
- **Motor symptoms:** none; may be associated with ALS in rare cases
- **Progression:** gradual but faster than AD
- **Lab tests:** normal
- **Imaging:** atrophy in frontal and temporal lobes
<table>
<thead>
<tr>
<th>Stage 1: No cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimpaired individuals experience no memory problems, and none is evident to a health care professional during a medical interview.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2: Very mild cognitive decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals at this stage feel as if they have memory lapses, especially in forgetting familiar words or names or the location of keys, eyeglasses, or other everyday objects. However, these problems are not evident during a medical examination or apparent to friends, family, or coworkers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3: Mild cognitive decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-stage Alzheimer disease can be diagnosed in some, but not all, individuals. Friends, family, or coworkers begin to notice deficiencies. Problems with memory or concentration may be measurable in clinical testing or discernible during a detailed medical interview.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4: Moderate cognitive decline (mild or early-stage Alzheimer disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At this stage, a careful medical interview detects clear-cut deficiencies. The affected individual may seem subdued and withdrawn, especially in socially or mentally challenging situations.</td>
</tr>
</tbody>
</table>
### Stage 5: Moderately severe cognitive decline (moderate or mid-stage Alzheimer disease)

Major gaps in memory and deficits in cognitive function emerge. Some assistance with day-to-day activities becomes essential.

### Stage 6: Severe cognitive decline (moderately severe or mid-stage Alzheimer disease)

Memory difficulties continue to worsen, significant personality changes may emerge, and affected individuals need extensive help with customary daily activities.

### Stage 7: Very severe cognitive decline (severe or late-stage Alzheimer disease)

This is the final stage of the disease when individuals lose the ability to respond to their environment, to speak, and ultimately to control movement.
PRIMARY GOAL OF TREATMENT

To enhance quality of life and maximize functional performance by improving cognition, mood, and behavior.
NONPHARMACOLOGIC MANAGEMENT (1 of 2)

- Cognitive rehabilitation
- Supportive individual and group therapy
- Physical and mental activity
- Regular appointments every 3–6 months
- Family and caregiver education and support
- Attention to safety
  - Need for supervision, wandering, driving etc.
• Environmental modification

  - Orientation and memory measures such as clocks, calendars, to-do list, visual clues, simple and compassionate communication style
PHARMACOLOGIC MANAGEMENT

- Treatment should be individualized
- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
- Memantine
- Other cognitive enhancers
- Antidepressants
- Psychoactive medications
CHOLINESTERASE INHIBITORS
(1 of 2)

• Slow breakdown of acetylcholine

• Clinical trials demonstrate modest delay in cognitive decline compared with placebo in AD

• GI side effects common
  - Mitigated by slow titration curve
  - Maximum dosing of donepezil 23 mg/day creates significant side effects without evidence of improving global function

• No evidence of difference in efficacy among drugs
Use in other dementias

- Widespread use in vascular dementia not recommended
- Behavioral disturbances in Lewy body dementia can benefit from treatment
- Rivastigmine is FDA-approved for mild to moderate dementia in Parkinson dementia
- Treatment in frontotemporal dementia may worsen agitation
MEMANTINE

- Neuroprotective effect is to reduce glutamate-mediated excitotoxicity
- Modest benefit on cognition, ADLs, and behavior in AD
- Limited effect on cognition and no evidence to support widespread use in vascular dementia
- FDA-approved for moderate to severe AD
- Common adverse events: constipation, dizziness, headache
OTHER COGNITIVE ENHANCERS

- **Vitamin E** (α–tocopherol) may lower rate of decline, but no evidence of cognitive improvement in AD
  - *No longer recommended* due to evidence of increased mortality with high-dose supplementation

- **Selegiline** may low rate of decline, but no evidence of cognitive improvement in AD

- **Ginkgo biloba** offers no benefit in slowing cognitive decline in MCI
SYMPTOM MANAGEMENT (1 of 2)

- Psychoactive medications
  - Behavioral disturbances best managed nonpharmacologically, eg, reducing overstimulation, environmental modification

- Antidepressants
  - Depressed mood, low appetite, insomnia, fatigue, irritability, agitation
  - Possibly effective for disinhibition and compulsive behaviors
  - Caution: falls and anticholinergic effects that may worsen confusion (ie, paroxetine)
SYMPTOM MANAGEMENT (2 of 2)

- **1\(^{st}/2^{nd}\)-generation antipsychotics**
  - Limited evidence of efficacy and increased risk of all-cause mortality in dementia
  - Should be used with caution in targeting delusions, hallucinations, and paranoia — frequently attempt to taper off

- **Valproic acid and carbamazepine**
  - Possible options, but with limited evidence and increased risk of mortality

- **Benzodiazepines and anticholinergic medications** should be *avoided*
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
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 and maximize function by improving cognition, mood, behavior

• Treatment may involve both medications and nonpharmacologic interventions

• Community resources should be used to support patient, family, caregivers
A 78-year-old man comes to the office for a follow-up visit; he is accompanied by his wife. Possible Alzheimer disease was diagnosed 8 months ago, at which time CT of the brain showed mild atrophy and moderately severe periventricular and subcortical white matter microvascular disease.

Medications include transdermal rivastigmine, aspirin 81 mg/day, and simvastatin. At today’s visit, score on the MMSE is 23 of 30, and his Clinical Dementia Rating is 1.0.
The patient’s wife expresses concern about his ability to drive safely. She sometimes feels nervous riding with him. She notes that he has stopped driving at night or when it rains, that he drives shorter distances and less often since he retired 5 years ago, and that he received a traffic citation about 4 years ago. He has had no accidents or additional citations since then.

When asked if he thinks he is a safe driver, the patient says, “I’m probably a little bit slower than I used to be, but overall I’d say yes, I’m still a perfectly safe driver.”
Which of the following is the strongest evidence of the patient’s risk for unsafe driving?

A. Patient’s self-restriction and situational avoidance
B. History of a traffic citation in the past 5 years
C. Spouse’s concern
D. Score ≤24 on MMSE
E. Patient’s self-rating of driving ability
Which of the following is the strongest evidence of the patient’s risk for unsafe driving?

A. Patient’s self-restriction and situational avoidance
B. History of a traffic citation in the past 5 years
C. Spouse’s concern
D. Score ≤24 on MMSE
E. Patient’s self-rating of driving ability