Disclosure

**Relevant Financial Relationship(s)**
None

**Off Label Usage**
None
Learning Objectives

• Review the clinical features of Alzheimer’s disease, Lewy body disease, frontotemporal disorders, and cognitive disorder due to vascular disease

• Understand how to work up patients presenting with cognitive complaints in primary care setting

• Understand when to refer to neurology and cognitive specialist

• Review of non-pharmacological interventions and FDA-approved medications for cognitive disorders
Overview: Definitions

- **Major neurocognitive disorder**
  - Replaces the term “dementia” in DSM-V.
  - Significant cognitive decline from prior level of functioning in ≥ 1 cognitive domains (attention, executive function, learning/memory, language, perceptual-motor, social) such that it *interferes with independence in at least complex daily activities*.
  - Significant objective impairment in cognition on standard testing.
  - Not due to delirium or another medical/mental condition.

- **Mild neurocognitive disorder**
  - Replaces the term “mild cognitive impairment” in DSM-V.
  - Cognitive decline does NOT *interfere with independence of daily activities*.
  - Modest degree of objective impairment in cognition on standard testing.
  - Not due to delirium or another medical/mental condition.

Overview: Common Etiologies

- **Degenerative:**
  - Alzheimer’s disease (most common)
  - Lewy body disease
  - Frontotemporal disorder(s)

- **Vascular:**
  - Multi-infarct
  - Subcortical
Alzheimer’s Disease

- **Most common cause of dementia**
- **Age**: Biggest risk factor
  - Incidence:
    - 1.3% per year (age > 65)
    - Doubles every 5 years after age 65
  - **Early-Onset**: Younger than age 65
  - Do **NOT** mix up “early-onset” with “early/mild-stage”
- Death within 3-9 years (on average) after diagnosis
  - 6th leading cause of death in the U.S. (2014)
- Prevalence: 4.7 million in the U.S (age 65 or older) in 2010
  - 13.8 million in the U.S. by 2050


Alzheimer’s Disease

- Insidious onset

- Gradual progression of impairment
  - Memory-predominant deficits on standard testing
  - Lacks clinical features to suggest other degenerative etiologies

- Pathology: β-amyloid

- Biomarkers:
  - CSF β-amyloid/tau ratio
  - MRI
  - FDG-PET; Amyloid-PET; Tau-PET
Lewy Body Disease: McKeith Criteria

Pathology: α-Synuclein

Supportive Clinical Features:
- Neuroleptic sensitivity
- Autonomic dysfunction

Core Features:
- Fluctuations
- Visual hallucinations
- REM sleep behavior disorder
- Parkinsonism (bradykinesia/rigidity > tremor)

Dementia

DLB: Parkinsonism

- Seen in 70-90% of patients
- Cognitive changes usually precede parkinsonism or are seen within one year from onset of parkinsonism

Farlow et al. UpToDate 2015.
REM sleep Behavior Disorder (RBD)

- 50-80% of DLB patients
- Can precede dementia onset by decades

Howell and Schenck. JAMA Neurol 2015.
Frontotemporal Disorder(s)

- Younger age of onset compared to AD and LBD

- **Behavior-variant**
  - Behavioral disinhibition: socially inappropriate, loss of manners, impulsive, lack of empathy, hyperorality, etc.
  - Prominent executive dysfunction. Other cognitive domains could be preserved in the beginning.

- **Language-variant**
  - Primary progressive aphasia
    - Difficulty with language is the primary feature and cause of functional impairment.
    - May involve non-language domains as disease progresses.

- Other: Corticobasal degeneration; Progressive supranuclear palsy

- Pathology: Tau

Cognitive disorder due to vascular disease

- **Multi-infarct**
  - Presenting symptoms depend on location of infarct(s)
  - Step-wise progression
  - CT/MRI – encephalomalacia/lacunar infarcts

- **Subcortical**
  - May or may not have focal findings on exam
  - Gait instability
  - Urinary symptoms not explained by urologic disease
  - Executive dysfunction > memory deficits
  - Could present as gradual progression instead of step-wise
  - CT/MRI – extensive white matter small vessel ischemic changes

Wright et al. UpToDate 2017.
Primary Care Providers: Critical Role

- **Identify** patients with cognitive symptoms

- **Rule out medical/mental conditions** that may cause cognitive disturbance (e.g. hypothyroidism, B12 deficiency, depression, etc.)

- Optimization of **risk factors management** (e.g. hypertension, hyperlipidemia, diabetes)

- Manage majority of dementia cases **longitudinally**
PCP: Case Identification

- Affordable Care Act: Medicare Annual Wellness Visit should include “detection of any cognitive impairment”.

- What to ask?
  - **WHEN did it start**: Make sure to ask specifically when the VERY FIRST sign of memory loss emerge, no matter how minor it seemed.
  - **HOW did it start**: Gradual versus Sudden.
  - **HOW did it change**: Progressive, Static, or Fluctuating.
  - **WHO noticed it**: Important to obtain collateral history from family/friends whenever possible.
  - **WHAT happened at onset**: Stroke, head trauma, neurological/systemic illnesses, hospitalization, surgery/general anesthesia, etc.
PCP: Case Identification

- Neurological exam
- Cognitive Screen: many options
- Lab workup:
  - Basic: TSH, B12, MMA, Vitamin D.
  - Syphilis serology if has history of high-risk sexual behavior or from areas with high prevalence
  - CBC/CMP if no recent baseline
  - Other labs as deemed necessary based on history
- Imaging:
  - Either done prior to neurology visit or after.
  - MRI most ideal if no contraindication.
PCP: When to refer

- Patients with *atypical presentations*:
  - Young/early-onset (age < 65)
  - Rapidly progressive
  - Other neurological signs and symptoms (e.g. seizures, focal deficits)
  - Suspicion of uncommon diagnoses (e.g. normal pressure hydrocephalus, autoimmune encephalopathy)

- Diagnosis uncertain (e.g. normal-aging versus neurodegenerative disease versus depression)
Treatments: Overview

- **Non-pharmacological**
  - Exercise
  - Diet
  - Nutritional Supplements
  - Cerebrovascular risk factors management

- **Pharmacological**
  - Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)
  - NMDA-receptor antagonist (memantine)
  - Combination therapy
Non-Pharmacological Interventions
Exercise

- Evidence for slowing down progression of functional decline, but no definitive benefit on cognition.
  - Rolland et al 2007:
    - 134 nursing home residents
    - Randomized to exercise program (1-hr session x 2/week x 12 months) or routine medical care
    - Exercise group showed **significantly slower decline in ADL score**
  - Pitkala et al 2013:
    - 210 home-dwelling patients
    - Randomized to group-based exercise, home-based tailored exercise programs, and controls
    - Exercise groups showed **significantly slower functional deterioration at 6 months and fewer falls**
  - Hoffmann et al 2015:
    - 200 mild-AD patients
    - Randomized to supervised moderate-to-high intensity aerobic exercise or control group
    - Exercise group showed **reduced neuropsychiatric symptoms**; in the subgroup exercising with high attendance and intensity there was also **significantly slower cognitive decline**.

Exercise

Koo et al. 2013.
Diet

- Mediterranean diet (31% lower relative risk)
  - Rich in n-3 polyunsaturated fatty acid (PUFA)
  - Vegetables, fruit, legumes
  - Moderate amount of fish
  - Low-moderate amount of red wine during meals
  - Olive oil
- Higher adherence is associated with lower mortality in AD.
Nutritional Supplements

- **Vitamin B group:** Controversial
  - 28% relative risk reduction (Meta-analysis, Cao et al 2015).
  - May slow down the atrophy of specific brain regions key to AD process and associated with cognitive decline in MCI patients (RCT, Douaud et al 2013).
  - High-dose folate/B6/B12 in 409 mild-moderate AD patients showed no benefit in cognition (RCT, Aisen et al 2008).

- **Vitamin D**
  - Deficiency: Meta-analysis showed ~2.4x relative risk of cognitive impairment.
  - Vitamin D Receptor (VDR): expressed in prefrontal cortex, cingulate gyrus, basal forebrain, caudate/putamen, thalamus, substantia nigra, LGN, hypothalamus, cerebellum.

Nutritional Supplements

- **Anti-oxidants**
  - **Vitamin E**: Controversial
    - 20% relative risk reduction (Meta-analysis, Cao et al 2015).
    - 2000 IU/day showed benefit in slowing down functional decline, but no benefit for cognition, in moderately-severe and mild-to-moderate AD patients, respectively. No additional benefit on top of memantine therapy (Sano et al 1997, Dysken et al 2014).
    - No convincing evidence that vitamin E is of benefit in the treatment of AD or MCI (Cochrane Systemic Review, Farina et al 2012).
    - **CAUTION**: High dose (≥ 400 IU/day) Vit E may have increased risk for all-cause mortality (also controversial).
  - Vitamin C and Flavonoids: No significant benefits in meta-analysis.

Reduce cerebrovascular risk factors

• Management of:
  – Smoking
  – High cholesterol
  – Diabetes mellitus
  – High blood pressure
  – Obesity
  – Sleep apnea

Cao et al 2015.
Pharmacological Interventions
Cholinesterase inhibitors: Overview

- **Mechanism:** Augment cholinergic activities in Central Nervous System

- **Donepezil, Galantamine, Rivastigmine**

- **FDA-approved for mild-moderate AD**
  - Donepezil: Also approved for severe AD (2006)

- **Similar efficacy between the three.**
  - Symptomatic therapy: improvement in cognition, function, and behavioral disturbance.
  - No survival benefits.

- **Similar adverse effect profiles**
  - GI (nausea, vomiting, diarrhea, loss of appetite), dizziness, headache, AV block, bradycardia

- **Choosing an agent:**
  - Cost: Formulary vs Non-formulary
  - Individual patient’s tolerability (may be different despite similar AE profiles)

Deardorff et al 2015; Suh et al 2011; Seltzer 2010; Herrmann et al 2009; Birks and Harvey 2006; Micromedex.
Cholinesterase inhibitors

- **Donepezil (Aricept ®) (1996)**
  - 5 mg daily → 4-6 weeks → Target 10 mg daily.
  - Moderate-Severe AD: can increase up to 23 mg daily (Some cognitive benefits but higher risk of adverse effects)

- **Galantamine (Razadyne ®) (IR – 2001, ER - 2004)**
  - IR: 4 mg BID → increase every 4-6 weeks → Target 12 mg BID.
  - ER: 8 mg daily → increase every 4-6 weeks → Target 24 mg daily.
  - IR versus ER: Pharmacologically equivalent. ER has better 1-year persistence (54%) than IR (44%).

  - Oral: 1.5 mg BID → increase every 2-4 weeks → Target 6 mg BID.
  - Transdermal: 4.6 mg/day → 4-6 weeks → Target 9.5 mg/day
    - 13.3 mg/day patch: approved for severe AD (ACTION study)
  - PO vs TD: TD is better tolerated with less GI adverse effects.
  - Also approved for dementia due to Parkinson’s disease

Adler et al 2014; Sadowsky et al 2010; Seltzer 2010; Herrmann et al 2009; Micromedex.
Cholinesterase inhibitors: Donepezil 23 mg

Farlow et al 2010.
NMDA-Receptor Antagonist

- **Mechanism**: Neuroprotection by reducing excitotoxicity due to CNS glutamate.

- **Modest benefits** in moderate-severe AD patients.
  - Delays functional and cognitive decline.
  - Improves behavioral disturbance.
  - Possibly disease-modifying.

- **Adverse effects**: Headache, confusion, dizziness, diarrhea

- **Memantine (Namenda ® - 2003, Namenda XR ® - 2010)**
  - Memantine: 5 mg daily → increase every 1 week → Target 10 mg BID.
    - Generic formulation available.
  - Memantine ER: 7 mg daily → increase every 1 week → Target 28 mg daily.
    - No generic version of yet

- **IR versus ER**: No direct comparison of efficacy. ER can be sprinkled in applesauce (dysphagia patients).

Matsunaga et al 2015; Plosker 2015; Reisberg et al 2003; Micromedex.
Combination Therapy

- Donepezil + Memantine
  - Improvement/delayed progression of cognition and function.
  - Some controversy about whether the modest benefits are clinically meaningful or not.
    - NICE (UK) meta-analysis: insufficient evidence to support combination therapy when compared with memantine therapy alone.

- Namzaric ® (donepezil-memantine 10-14 mg or 10-28 mg, once daily) – Approved 12/2014
  - Brand-name only
  - No Phase III trial for Namzaric per se. Approval based on prior trials for memantine ER and donepezil.

Treatment: Variations

- **LBD:**
  - May show greater response to cholinesterase inhibitors than AD
  - Same pharmacological therapy strategy as AD.

- **Vascular cognitive disorder:**
  - Same pharmacological therapy strategy as AD

- **FTD:**
  - No definitive evidence to support the use of cholinesterase inhibitors or memantine.
  - Some report of potential worsening of cognitive/behavioral symptoms on cholinesterase inhibitors or memantine
  - Trial of cholinesterase inhibitors may still be pursued if AD remains a possible differential

Lee SE and Miller BL. UpToDate 2016.
SUMMARY

• Distinguish common etiologies of cognitive disorder in geriatric population:
  – Alzheimer’s disease: Insidious onset, memory-predominant deficit
  – Lewy body disease: McKeith Criteria
  – FTD: Behavior versus language variants
  – Vascular: History of stroke/TIA and supporting CT/MRI findings

• Primary care providers play a critical role in the management of cognitive disorders:
  Identification; Rule out other conditions; Longitudinal follow-ups; Referral of unusual cases

• Exercise, Mediterranean diet, control of cerebrovascular risk factors, and possibly vitamin B/D/E supplementation are beneficial in patients with cognitive disorders.

• Cholinesterase inhibitors (donepezil, galantamine, rivastigmine), NMDA-Receptor antagonist (memantine), and combination therapy are indicated for Alzheimer’s disease, Lewy body disease, and vascular cognitive disorder (choice depends on the stage/severity).
Thank you!

Questions?