ADVANCED INSIGHTS INTO THE PREVENTION, TREATMENT AND MANAGEMENT OF ALZHEIMER’S DISEASE

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I have no relevant financial disclosures
Objectives

Upon completion of this activity participants should be able to:

• Discuss the current status of Alzheimer’s disease
• Identify the diagnosis and placement of therapeutic options used for the treatment of agitation in patients with Alzheimer’s disease
• Explore the role of biomarkers, tools, and imaging for current use in the diagnosis of Alzheimer’s disease
• Analyze emerging therapeutic options that can achieve new treatment targets in patients who do not respond to traditional therapies

CLASSIFICATION OF ABNORMAL COGNITIVE STATES

SUBJECTIVE Memory Complaints
No Cognitive or Functional deficits

MILD Cognitive Impairment (MCI)
Memory complaints, some cognitive deficits but No functional Deficits.

DEMENTIA
Cognitive + Functional Deficits
Incorporating Assessment of Cognition During the Annual Wellness Visit (AWV)

- Annual unstructured (patient and informant based) and structured cognitive assessments could be used to monitor significant changes in cognition
- Observation by clinicians (medical and associated staff) are important
- Potentially lead to a new diagnosis of dementia for those with MCI or new recommendations for medical and overall care for those with dementia
- **Explain to patients:** “This is something I do for all of my older patients as part of their annual visit.”
- If the initial assessment prompts further evaluation, avoid explanation of results until a more comprehensive evaluation has been completed
The two-visit approach is a time-effective process to evaluate suspected dementia in primary care

Regardless of the timing and setting, clinicians are encouraged to counsel patients to include an informant in the diagnostic process.

- Complete medical history
- Physical and neurological exam
- Assessment for depression
- Exclude delirium
- Review for medications that affect cognition.

Assessment of multiple cognitive domains
- ADL and IADL functioning
- Standard laboratory tests
- Structural brain imaging
- Neuropsychological testing

Differentiating AD From Other Causes of Cognitive Impairment Is Challenging

- Mild cognitive impairment (MCI) can be confused with normal aging
- Differentiating degenerative or vascular etiologies from reversible ones is important
- Patients often present with multiple comorbidities, which can contribute to confusion about their diagnoses
- About 1 in 5 AD dementia diagnoses by experts do not have AD

Causes of cognitive impairment include

- Depression
- Delirium (e.g. infection)
- Thyroid dysfunction/ B12 deficiency
- Vascular dementia/stroke
- Parkinson’s disease
- Lewy body dementia
- Frontotemporal dementia
- Alzheimer’s disease
- Normal pressure hydrocephalus
- Substance or alcohol abuse
- Wernicke-Korsakoff’s syndrome
- Creutzfeld-Jakob’s disease
- Tumor
- HIV related dementia
- Sleep deprivation/ disorder

Cognitive or neuropsychiatric symptoms that

1. Interfere with the ability to function at work or at usual activities
2. Represent a decline in patient’s level of functioning
3. Cannot be explained by delirium or major psychiatric disorder
4. (cont. on next slide)

Reaching a clinical diagnosis – cont.

4. Involve a minimum of 2 of the following domains
   - Ability to acquire and remember new information
     Misplacing items, forgetting appointments, getting lost on a familiar route
   - Reasoning and handling of complex tasks, and judgment
     Poor decision-making ability, poor understanding of safety risks
   - Visuospatial abilities
     Inability to recognize faces or objects, inability to orient clothing to body
   - Language functions
     Difficulty thinking of common words while speaking; speech, spelling, and writing errors
   - Changes in personality, behavior
     Uncharacteristic mood fluctuations, apathy, social withdrawal, socially unacceptable behaviors
NIA/AA Core Clinical Criteria of Alzheimer’s Disease Diagnosis

According to the 2011 National Institute of Aging/Alzheimer’s Association (NIA/AA) guidelines, Alzheimer’s disease diagnosis requires core criteria be met1,2

1. Report of cognitive concern by patient, caregiver, or clinician
2. Gradual onset over months to years
3. Evidence of longitudinal cognitive decline
4. Differential diagnosis that rules out vascular, traumatic, and medical causes of cognitive decline

Objective evidence of impairment in ≥1 cognitive domains and maintains independence

MCI due to AD

Dementia due to AD

Possible AD:
- Apical course or diagnostically mixed presentation

Probable AD:
- Insidious onset, history of progressive worsening, & no evidence of CVD, DBS, FTD, or aphasia

Proven AD:
- Meets widely accepted neuropathology criteria at autopsy


Standard Laboratory Tests

- thyroid-stimulating hormone (TSH)
- complete blood count (CBC)
- serum B12, folate
- complete metabolic panel,
- testing for sexually transmitted diseases (HIV, syphilis) if at risk

Structural brain imaging, including MRI or CT, is a supplemental aid in the differential diagnosis of dementia, especially if abnormal neurologic findings are noted
- especially informative in dementia of recent onset and progressive
- younger onset dementia (65 years of age)
- history of head trauma
- or neurologic symptoms suggesting focal disease

C.B. Cordell et al. / Alzheimer’s & Dementia 9 (2013)
Treatment

Goals of Treatment in Dementia

- Improve or preserve ADL function
- Reduce caregiver burden
- Enhance quality of life, safe environment, and social engagement

- Improve or preserve cognitive function
- Enhance mood and behavior
- Slow deterioration
- Manage psychiatric and behavioral symptoms
### FDA-Approved Drugs; none slows neuronal loss or destruction

<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>Excelon</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>

- donepezil, galantamine, rivastigmine = Cholinesterase inhibitors
- Memantine = NMDA receptor antagonist

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### Behavioral and Psychotic Symptoms of Dementia (BPSD)

- **Examples:** depression, hallucinations, agitation, aggression, wandering, “sun-downing”
- 90% of persons with dementia develop one BPSD
- Commonly manifested in moderate to severe disease
- Lead to caregiver stress and frustration
- Often the breaking point prior to institutionalization
- BPSD often the impetus to **weight loss, falls, infection and incontinence**
- No FDA-approved treatments for BPSD
- Antipsychotics, antidepressants and anticonvulsants used off label (some benefit with antipsychotics); **consider if BPSD poses greater risk to individuals and families**
### Non-pharmacological Approaches

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Medical evaluation</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel with them</td>
<td><strong>Assess for pain, constipation, infection, vision, hearing</strong></td>
<td><strong>Routine physical activity</strong></td>
</tr>
<tr>
<td>Don’t disagree, respect</td>
<td><strong>Review medications</strong></td>
<td><strong>Optimize nutrition and meal experience</strong></td>
</tr>
<tr>
<td>Eye contact, allow space</td>
<td><strong>Assess for depression, sleep disorder</strong></td>
<td><strong>Maintain daily routine</strong></td>
</tr>
<tr>
<td>Slow calm voice</td>
<td><strong>Remove triggers (overstimulation, caregivers)</strong></td>
<td><strong>Enjoyable activities, comfort food</strong></td>
</tr>
<tr>
<td>Avoid scolding, threatening...</td>
<td><strong>Evaluate risks v. benefits of antipsychotics</strong></td>
<td><strong>Reminiscing, art, spirituality, aroma therapy</strong></td>
</tr>
<tr>
<td>Validate and reassure</td>
<td></td>
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</tbody>
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### Pharmacological considerations

- FDA weighed in that treatment of behavioral disorders with antipsychotics is associated with increased mortality
- 17 placebo-controlled trials showed significant benefit in aggression at 12 wks but 1.6-1.7x inc risk for mortality (infections and CV causes)
- First generation antipsychotics are felt to have equivalent risks (haloperidol)
- All antipsychotics have a **BLACK BOX WARNING**
- Decrease in NH antipsychotic use using educational OASIS model (ARR 3.9%)—Blanks et al. JAMA Int Med 4-17
Beyond Beers:

**Antipsychotics**
- Neuroleptic Malignant Syndrome
- Extrapyramidal Symptoms
- Cerebral Adverse Events
- Falls
- Sedation
- QTc Prolongation
- Sudden Death

**Benzodiazepines**
- Depression
- Confusion
- Stroke/Cerebral Adverse Events
- Falls/Fractures
- Sleep Disturbance
- Delirium

Managing Cardiovascular Risk and Stroke Prevention—Low Hanging Fruit

- Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of dementia
- **Smoking, obesity in midlife and diabetes**: some evidence that **impaired glucose processing** (a precursor to diabetes) may also result in an increased risk
- **Hypertension and high cholesterol** in midlife also implicated as risk factors
- Conversely, factors that protect the heart may also protect the brain and reduce the risk of developing AD or other dementias
  - **Physical activity**
  - Consuming a **diet lower in saturated fats**

_Rusanen. Arch Int Med 2011;171_
_Ronnemaa. Dement geriatr Cogn Disord 2011;31_
Assessing the risk of dementia with diabetes

- Metanalysis of 16 studies
- Incidence of any dementia was increased in people with diabetes in 5 of 7 studies
- Overall, the incidence of dementia was increased by 50-100% relative to people without diabetes (CV factors not controlled in all)
- Increased risk of Alzheimer's disease by 50-100% (7 of 11 studies)
- Increase in risk of vascular dementia of 100-150% (6 of 7 studies)

Biessels et al. Lancet Neurology 5(1); Jan 2006

Mechanisms that may link diabetes and dementia

Predictors of cognitive impairment and dementia in older people with diabetes

- Surviving participants of the Fremantle Diabetes Study (FDS), who were aged 70 years
- Of 302 participants, 28 (9.3%) had dementia (16 with probable AD) and 60 (19.9%) had cognitive impairment without dementia
- The major independent longitudinal predictors of dementia were
  - *older age* (per decade; odds ratio 4.0)
  - *diabetes duration* (for each 5 years; odds ratio 1.69)
  - *peripheral arterial disease* (odds ratio 5.35)
  - exercise (which was protective; odds ratio 0.26)
- For Alzheimer’s disease, diabetes duration was an independent predictor in addition to age and diastolic blood pressure

Bruce et al. Diabetologia Feb 2008

Brain Changes Associated with Alzheimer’s Disease
May begin 20 y before symptoms are evident

Collapsed Tau protein=TANGLES
Clumped beta-amyloid protein = PLAQUES
Alzheimer cells
healthy cells
Normal Preclinical MCI Dementia

Abnormal

Clinical Disease Stage

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/sMRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

R.A. Sperling et al. Alzheimer’s & Dementia; (2011) 1-13

Bateman et al. NEJM. July 2012
Functional Imaging

- PET scanning with fluorodeoxyglucose (FDG –PET) indicates that AD is associated with reduced glucose uptake in brain areas important for memory, learning and problem solving
- However patterns of reduced activity do not translate to diagnostic information about individuals

Molecular Imaging

- Most active area of research; may provide biological clues to disease before changes in brain structure and function affect memory
- Four compounds approved for highlighting deposits of beta-amyloid (PIB, Florbetapen, Florbetapir, Flutametamol)
- May help monitor disease progression and effectiveness of next generation disease-modifying treatments
- Clinical trials underway to test radiotracers for Tau protein
Appropriate Criteria for Amyloid Imaging

- Patients with persistent or progressive unexplained MCI
- Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation
- Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

Amyloid imaging is **inappropriate** in the following situations:
- Patients with core clinical criteria for probable AD with typical age of onset
- To determine dementia severity
- Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE)ε4?
- Patients with a cognitive complaint that is unconfirmed on clinical examination
- In lieu of genotyping for suspected autosomal mutation carriers

K. Johnson et al. JNM 2013

The Accuracy of CSF Biomarkers for the Diagnosis of Alzheimer’s Disease—metanalysis

- Overall accuracy greatest when CSF biomarkers were used to discriminate AD from normal controls
- Biomarker ratios had higher accuracy than single biomarkers (Ab42/Tau ratio sens 0.96 at spec 0.80) was more accurate than Tau alone
- Phosphorylated Tau (pTau) was significantly more accurate than Ab42 and Tau, in discriminating AD from non-AD dementias
- Consensus: changes in Ab42, t Tau, and pTau allow diagnosis of AD in its prodromal stage (if all three are normal, AD is ruled out) Molinuevo et al. Alzheimer’s and Dementias, Vol 10, issue 6, 2014
- Problem is measurement variability; AA funded QC program for CSF biomarkers
Emerging Therapeutic Options

- The A4 trial is studying effectiveness of solenazumab (targeting beta-amyloid) on 1150 asymptomatic individuals with high levels of amyloid on PET scans
- TOMORROW Trail—will explore use of pioglitazone in 3500 asymptomatic individuals with APOE-e4 or TOMM40 risk gene
- ALHEIMERS PREVENTION INITIATIVE (API)—gene mutation positive people with be treated with crenezumab to deliver antibodies against beta-amyloid
- Alzheimers Association Trail Match provides individualized services to match volunteers with trials

In Summary

- Alzheimer’s disease will almost triple in people over 65 by 2050
- A structured clinical and laboratory evaluation can be performed in the primary care setting
- Currently there is no cure; good medical care and non-pharmacological management of mood and behavior matters
- Optimizing cardiovascular risks can reduce the development of dementia
- Studies focusing on treatment of asymptomatic individuals may be the next frontier
QUESTIONS?
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