The Latest Buzz in Diagnosis and Treatment of Cognitive Disorders

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1/21/23
Disclosures

Grants:
Avanir
Biohaven
BioVie
Cassava
Cerevel Therapeutics
Cognition Therapeutics
Eisai
Genetech
InSightec
Janssen
Precision Medicine
Roche
UCB Biopharma
uniQure
Vivoryon Therapeutics

Consultant:
Acadia
Biogen
Brain Test
Eisai
Medscape/WebMD
Vascular Scientific
Learning Objectives

- Discuss diagnosis of common dementia conditions
- Learn about management approaches for the patient with cognitive disorders
- Review new treatments for Alzheimer’s and Lewy body disorders
Normal

Mild Cognitive Impairment

Dementia
Prevalence of Dementia Syndromes

AD = Alzheimer’s disease; DLB = Dementia with Lewy bodies; FCD = Focal cortical degeneration
Steps in Differential Diagnosis

- History
- Physical Exam
- Mental Status Exam
- Behavioral and Psychiatric symptoms
- Laboratory Evaluations
- Neuroimaging
History

- Onset
- Clinical course
- Past medical history
- Psychiatric illness
- Medications
- Social and family history
Physical Exam

Normal:
- AD
- FTD
- Depression

Apraxia Only:
- AD
- FTD
- NPH (gait apraxia)

Movement, tone, and gait abnormalities:
- Vascular dementia
- Dementia with Lewy bodies
- Parkinson’s disease dementia
- Huntington’s disease
- Rapidly evolving dementias

AD = Alzheimer’s disease; FTD = Frontotemporal dementia; NPH = Normal pressure hydrocephalus
Mental Status Exam

- Attention
- Language
- Memory
- Visuospatial skills
- Abstraction and calculations
- Judgment and executive function
- Personality and emotional state
Cortical vs Subcortical

Speech

- **Cortical:** Normal, Stereotypy
- **Subcortical:** Hypophonic, dysarthric

Language

- **Cortical:** Anomia, aphasia
- **Subcortical:** Normal
Cortical vs Subcortical

Memory

- **Cortical**: Amnesia
- **Subcortical**: Retrieval deficit (forgetful)

Cognition

- **Cortical**: Acalculia, impaired attention
- **Subcortical**: Slow processing speed, distraction
Cortical vs Subcortical

Executive

- **Cortical**: Impaired sequencing, apraxia, poor judgment & insight, ↓ verbal fluency

- **Subcortical**: Similar only if frontal-subcortical nuclei circuits involved

Visuospatial

- **Cortical**: Abnormal orientation and constructions

- **Subcortical**: Abnormal constructions
Construction Tests
Mental Status

Cortical:
- AD
- bvFTD: spares posterior cortical deficits

Subcortical:
- Depression
- Vascular dementia
- NPH
- Parkinson’s disease dementia
- Huntington’s disease

Mixed Cortical and Subcortical:
- Vascular dementia
- Dementia with Lewy bodies
- Rapidly evolving dementias

AD = Alzheimer’s disease; FTD = Frontotemporal dementia; NPH = Normal pressure hydrocephalus
Barriers to Early Diagnosis of MCI and Dementia

- Patients with MCI and early dementia have impaired insight
- First present to the doctor an average of 3.5 years after cognitive symptoms start
- Physicians may not notice subtle cognitive deficits in routine office visits
- Often too much time or personnel resources required to administer testing

Brief Multi-domain Cognitive Assessment Tools

- Preference is to have tools that are practical, relevant, easy to use, and require minimal training

- Examples:
  - Mini-Mental State Examination (MMSE)\(^1\)
  - Montreal Cognitive Assessment (MOCA)\(^2\)
  - AD8 informant interview\(^3\)
  - Saint Louis University Mental Status examination (SLUMS)\(^4\)
  - Self-Administered Gerocognitive Examination (SAGE)\(^5\) or the digital equivalent BrainTest\(^6\)

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## Comparative features of assessment tools

<table>
<thead>
<tr>
<th>Features</th>
<th>MMSE</th>
<th>MoCA</th>
<th>AD8</th>
<th>SLUMS</th>
<th>SAGE/BrainTest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scoring range</strong></td>
<td>0-30 Higher score better</td>
<td>0-30 Higher score better</td>
<td>0-8 80% with cutoff 2 or more</td>
<td>0-30 Higher score better</td>
<td>0-22 Higher score better</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Clinician with patient</td>
<td>Clinician with patient</td>
<td>Clinician with informant and patient</td>
<td>Clinician with patient</td>
<td>Patient (self-administered); SAGE (paper), BrainTest (digital, tablet)</td>
</tr>
<tr>
<td><strong>Time to administer</strong></td>
<td>7-10 minutes</td>
<td>10-13 minutes</td>
<td>3 minutes</td>
<td>10 minutes</td>
<td>10-15 minutes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$1.23 to PAR</td>
<td>free</td>
<td>free</td>
<td>free</td>
<td>SAGE: free BrainTest $25</td>
</tr>
<tr>
<td><strong>Specificity/ sensitivity to detect dementia</strong></td>
<td>84%/78% with cutoff 26 or less</td>
<td>87%/100% with cutoff 25 or less</td>
<td>80%/84% with cutoff 2 or more</td>
<td>Comparable to MMSE but better at detecting mild Neurocognitive Disorders</td>
<td>95%/95% with a cutoff of ≤ 16 to detect dementia and 95%/79% (90%/71%, BrainTest) with a cutoff of ≤16 (15, BrainTest) to detect cognitive impairment</td>
</tr>
</tbody>
</table>
Increased Website Traffic

- The Wexner Medical center site had more visits in a single day on 1.13.14 than any other day over the last 10 years!
- The SAGE page had 181,000 pageviews on 1.13.14 which was a 17,000% increase from the prior day.
- SAGE/BrainTest web page remains the most visited in all of OSU Web presence since 2014.

SAGE Test demonstrates high level of promotional sensitivity

Source: NBC Los Angeles, NBC4 News at 5 p.m. on Jan. 13, 2014

NBC Nightly News and the Today Show

CBS National News

Fox News
SAGE/BrainTest: Domains

Score range: 0-22

Orientation
• Month, date, year (4 points)

Language
• Picture naming (2 points)
• Verbal fluency (2 points)

Calculations (2 points)

Visuospatial
• Copying 3-D constructions (2 points)
• Clock draw (2 points)

Executive
• Modified trails B (2 points)
• Problem solving task (2 points)

Abstraction (2 points)

Memory (2 points)

Evaluates Multi Domains and Global Cognition
SAGE: Change Over Time

- Significant Drop in SAGE Scores Revealed Dementia Conversion from MCI
- SAGE Scores of SCD Patients Were Significantly Higher than MCI Non-converters

SAGE Least Squares Mean Scores With Standard Error Bars

SAGE/BrainTest: for the Early Detection of Cognitive Impairment at PCP Visits

SAGE/BrainTest Usage Resulted in 6-Fold Detection of New Cognitive Conditions/Concerns

When SAGE was Utilized:

- PCPs documented detection of new cognitive conditions/concerns 6 times as often
- 9% vs 1.5%
- $p=0.003$

Scharre et al. American Academy of Neurology 2021 Annual Meeting Poster Presentation
9. Write down the names of the letters in the following sequence (be very careful about spelling):

   ________
   ________
   ________
   ________

10. Do the following: Draw a line from Start to 1, then to A, then to B, then to 2, then to B, then to 3, and alternate letters in order before ending at F (1 to A to B to 2 to B to 3 and alternate...
Consider a Staged Approach to Screening

Cognitive Concern or Age over 65?

- YES: SAGE/BrainTest
  - <17: Schedule appointment with patient and informant
    - A08 > 1 MOCA < 26: Consider dementia evaluation
    - A08 < 2 MOCA > 26: Re-screen in one year or consider neuropsychological testing
  - 17-22: Screen if concerns

- NO: Re-screen if concerns

Age over 80?

- YES: Re-screen every 6 mos.
- NO: Re-screen yearly

Scharre et al. Alzheimer Dis Assoc Disord 2010;24:64-71 at SAGEtest.osu.edu;

The Ohio State University
Wexner Medical Center
Laboratory Evaluation

Recommended for all dementias

- CBC
- Electrolytes, calcium, glucose, BUN, creatinine, LFT
- B12, folate
- TSH, T4
- FTA
Optional Evaluations
Consider for rapidly evolving dementias

- Sed rate, inflammatory markers
- HIV, Lyme
- CXR, EKG
- Urinalysis
- Assays for heavy metals, toxins
- LP
- EEG
Biomarkers in AD

- Amyloid-β: CSF/amyloid PET
- Synaptic dysfunction: FDG-PET/fMRI
- Tau-mediated neuronal injury: CSF/tau PET
- Brain structure: volumetric MRI

Elevated CSF tau and low Aβ42 is 95% specific and 60% sensitive for AD

Blood Biomarkers in AD

- Plasma biomarker tests are not currently FDA approved
  - Preliminary studies have shown differences in plasma concentrations of Aβ42 and Aβ42/40 ratio, t-tau, and p-tau in patients with AD compared with cognitively normal controls

- PrecivityAD test
  - CLIA approved; not FDA approved; validation results not published
  - Looks at amyloid beta 42/40 ratio and ApoE proteotype (similar to Apo E genotype)
  - Reported specificity is 77% and sensitivity 92%

- Plasma biomarker p-tau tests are not currently clinically available
  - p-tau181: predicted progression to AD
  - P-tau 217: increased in subjects before cognitive impairment or tau PET scans and at same time as tau CSF

Gray Matter Reductions in AD Using Voxel Based Morphometry

Alexander GE et al., ADNI MRI Core Team, 2007
Typical AD PET Scan

Normal Brain

AD Brain

Provided courtesy of M. Mega, MD, PhD, Department of Neurology, UCLA School of Medicine.
Amyloid PET Imaging

Jagust W. et al., ADNI-GO PET Core Team, 2011
Amyloid PET Imaging

Jagust W. et al., ADNI-GO PET Core Team, 2011
Amyloid PET and Tau PET

<table>
<thead>
<tr>
<th>Clinically Normal</th>
<th>PiB Aβ</th>
<th>Clinically Normal</th>
<th>T807 Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ-neg</td>
<td>DVR=1.0</td>
<td>Aβ-pos</td>
<td>SUVR=1.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

AD Dementia Aβ-pos
Dopamine Transporter SPECT DaTscan for Lewy body dementia/Parkinsonism

Surendranathan A, O’Brien JT. Evidence-Based Mental Health 2018;21:61-65
Imaging Normal DaTscan
Imaging Abnormal DaTscan
Diagnosis of AD

Stages¹

- **Preclinical stage²**: No clinical or cognitive symptoms but AD brain pathology has started (amyloid and tau proteins accumulation, cellular changes)

- **Mild Cognitive Impairment due to AD (Prodromal AD)³**: Decline from baseline cognitive abilities that are not so severe that they need hands-on assistance for daily activities they usually do themselves plus AD brain pathology

- **AD Dementia⁴**: Decline from baseline cognitive abilities that are severe enough to require hands-on assistance for daily activities they usually did for themselves plus AD brain pathology

Dementia with Lewy Bodies: Clinical Criteria

- Essential feature: Dementia
- Core clinical features:
  - Fluctuating cognition/attention/alertness
  - Recurrent visual hallucinations
  - REM sleep behavior disorder (may precede cognitive decline)
  - 1 or more features of Parkinsonism (bradykinesia, rest tremor, or rigidity)

McKeith et al. Neurology 2017;89:88-100
Dementia with Lewy Bodies: Clinical Criteria

- Supportive clinical features:
  - Severe neuroleptic sensitivity
  - Postural instability
  - Repeated falls
  - Syncope or other transient unresponsive episodes
  - Severe autonomic dysfunction (constipation, orthostatic hypotension, urinary incontinence)
  - Hypersomnia
  - Hyposmia
  - Hallucinations in other modalities
  - Systematized delusions
  - Apathy, anxiety, and depression

McKeith et al. Neurology 2017;89:88-100
Cognitive Rx in AD

Efficacy of Cholinesterase Inhibitors

• Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne)
• All of them work
• Up to 80% of patients show no decline after 6 months of treatment; 50% no decline after 1 year
• Need to give for ≥ 12 months to determine utility
• Always titrate to highest dose
Galantamine: 36-month Change From Baseline in ADAS-cog/11

Mean Change From Baseline ± SE in ADAS-cog/11

Cognitive Rx in AD

NMDA Antagonists: Memantine (Namenda)

- N-methyl-D-aspartate (NMDA) antagonists potentially prevent neuronal injury by reducing excitatory amino acid toxicity by glutamate
- Give in addition to cholinesterase inhibitor
- Side effects include headache, dizziness, fatigue, confusion
Results: Cognition – SIB

Memantine + Donepezil Produced Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone

![Graph showing mean change from baseline in SIB score over treatment weeks, with significant p-values marked (P=.057, P=.030, P<.001, P=.006, *P<.001 †P<.001).](image)


Data on file, Forest Laboratories, Inc.
Aducanumab/Lecanemab

- Human immunoglobulin G1 monoclonal antibody
- Aducanumab (ADU) binds to soluble aggregated (oligomers and fibrils), lecanemab (LEC) to soluble protofibrils and both to insoluble forms of Aβ
- Phase 3 Trials: 18 month, randomized, double-blind, placebo-controlled (ADU, n=3285; LEC, n=1795)
- ADU high dose (up to 10 mg/kg) and low dose (up to 6 mg/kg) and placebo: randomized 1:1:1
- LEC (100 mg/ml) and placebo; randomized 1:1
- Primary Endpoint: CDR-SB at 18 months
- Secondary Endpoints: MMSE, ADAS-cog 13 (14 and ADCOMS for LEC), ADCS-ADL-MCI, biomarkers

### Top Line Cognitive and Functional Findings primary & secondary endpoints, week 78

<table>
<thead>
<tr>
<th></th>
<th>Aducanumab(^1)</th>
<th>Lecanumab(^2)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo decline</td>
<td>High dose difference vs.</td>
</tr>
<tr>
<td></td>
<td>(n=548)</td>
<td>placebo (%) p-value (n=547)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>1.74</td>
<td>0.39 (-22%) 0.0120</td>
</tr>
<tr>
<td>MMSE or ADCOMS</td>
<td>-3.3 (MMSE)</td>
<td>0.6 (-18%) 0.0493</td>
</tr>
<tr>
<td>ADAS-Cog 13/14</td>
<td>5.162</td>
<td>-1.400 (-27%) 0.0097</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>-4.3</td>
<td>1.7 (-40%) 0.0006</td>
</tr>
</tbody>
</table>

2. Van Dyck et al, NEJM. 2022; DOI:10.1056/NEJMoa2212948
Aducanumab

Van Dyke. Biol Psychiatry 2018;83:311-3219
Top Line Adverse Event Findings

- Discontinuation of treatment rates: ADU: 25% high dose, 16.3% placebo; LEC: 7%; 3% placebo
- AE: ADU High dose 91%, placebo 87%; LEC 89%, placebo 82%
- SAE: ADU High dose 12.4%, placebo 13.4%; LEC 14%, placebo 11.3%
- Deaths: ADU High dose 8, placebo 6; LEC 6, placebo 7
- ARIA-E: ADU High dose 34.8%, placebo 2.6%; LEC 12.6%, placebo 1.7%
- ARIA-H microhemorrhage: ADU High dose 18.1%, placebo 6.3%; LEC 14%, placebo 7.7%
- 98% (ADU) and 94% (LEC) of the time the MRI findings of ARIA E resolved
- Apo E4 status ADU: positive had 42% and negative had 20% ARIA-E
- Apo E4 status LEC: positive had 15.8% and negative had 5.4% ARIA-E
- Symptomatic ARIA: ADU High dose 24.4%, placebo 5.6%
- Symptomatic ARIA: LEC 2.8%, placebo 0%
Amyloid Related Imaging Abnormalities: ARIA-Edema (ARIA-E)
ARIA-Hemorrhage (ARIA-H)
ARIA-superficial siderosis
## ARIA MRI Classification Criteria

<table>
<thead>
<tr>
<th>ARIA Type</th>
<th>Radiographic Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>ARIA-E</td>
<td>FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location &lt; 5 cm</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>≤ 4 new incident microhemorrhages</td>
</tr>
<tr>
<td>ARIA-H superficial siderosis</td>
<td>1 focal area of superficial siderosis</td>
</tr>
</tbody>
</table>
ARIA findings and infusion holding or discontinuation

Amyloid Related Imaging Abnormalities (ARIA)

If ARIA is present, careful clinical evaluation should be performed prior to continuing treatment

Asymptomatic Severe ARIA-H
- Discontinue aducanumab

Symptomatic ARIA (ARIA with Clinical Symptoms)
- The dose should be temporarily suspended
- Obtain MRI with diffusion weighted, FLAIR, and T2* GRE or SWI every 4 weeks until resolution of clinical symptoms and resolution of ARIA-E or until the MRI demonstrates radiographic stabilization of ARIA-H (i.e., no increase in size or number of ARIA-H) prior to restarting infusion

Asymptomatic Moderate to Severe ARIA-E or Moderate ARIA-H
- The dose should be temporarily suspended
- Obtain MRI with diffusion weighted, FLAIR, and T2* GRE or SWI every 4 weeks until resolution of ARIA-E or until the MRI demonstrates radiographic stabilization of ARIA-H (i.e., no increase in size or number of ARIA-H) prior to restarting infusion

Asymptomatic Mild ARIA-E or Mild ARIA-H
- Continue infusions at current schedule with caution
- Obtain MRI diffusion weighted, FLAIR, and T2* GRE or SWI every 4 weeks until resolution of ARIA-E or until radiographic stabilization (i.e., no increase in size or number of ARIA-H) appreciated

Dosing suspended for < 3 doses?
- Suspended < 3 doses: Continue infusions at current schedule
- Suspended ≥ 3 doses: Resume at a dose level one step below that previously administered

FDA Prescribing Information sheet, 2021 modified using clinical trial criteria (Haeberlein et al. Neurology. 2020;16(Suppl. 9):247-250)
Current Approved Treatments for DLB

- Rivastigmine approved for PDD by FDA
- Donepezil approved for DLB in Japan
- Memantine not approved; a few studies with trends
- Hints that cholinesterase inhibitors and memantine may have disease modifying characteristics
Promising Treatments for DLB: Neflamapimod

- Neflamapimod: a small molecule inhibits mitogen-activated serine/threonine protein kinase (p38 MAPK alpha)
- 2020 Positive (improved cognitive composite) phase 2 trial for mild to moderate DLB
- Intra-cellular enzyme p38 MAPK alpha stimulates pro-inflammatory cytokines by microglia producing inflammation-induced synaptic toxicity
Center for Cognitive and Memory Disorders – Trials

- Novel therapeutic medication trials for Mild Cognitive Impairment (MCI) progressing to AD
  - Monoclonal antibody against amyloid
  - Monoclonal antibody against tau (does not enter cells)
  - Transdermal nicotine for patients with MCI
  - Treating Glutamate dysfunction in Alzheimer’s disease
  - Treatment trials to improve synaptic density and health
  - Anti-inflammatory agents to treat AD
  - Varoglutamstat to reduce N3pE, a toxic form of the amyloid protein activating inflammation
  - CT1812 to target and displace amyloid oligomers bound to neuronal receptors
Center for Cognitive and Memory Disorders – Trials

- Innovative therapeutic device clinical trials for AD:
  - Deep Brain Stimulation – Neuropacemaker inserted into the frontal lobes on both sides to improve cognitive, behavioral, and functional impairments in AD subjects
  - Low intensity focused ultrasound – temporary breakdown of blood brain barrier designed to remove amyloid from the brain: active study
  - BDNF (brain derived neurotrophic factor) gene therapy phase I, first in human clinical trial AAV2 vector-mediated delivery to entorhinal cortex for MCI due to AD or mild AD dementia
Center for Cognitive and Memory Disorders – Trials

- Discovering new treatments for the behavioral disturbances in dementia:
  - Escitalopram for agitation
  - Dextromethorphan/quinidine for the treatment of agitation in patients with AD
  - CVL-871 is a dopamine D1 receptor partial agonist for the treatment dementia related apathy
Center for Cognitive and Memory Disorders – Trials

- Discover, standardize, and validate biomarkers for AD treatment trials:
  - ADNI4
  - Banking serum and cerebrospinal fluid for future studies in patients with dementia with Lewy bodies, vascular dementia, frontotemporal dementia, MCI, and Alzheimer’s disease

- Trial-ready cohort for preclinical/prodromal Alzheimer's disease:
  - Global Alzheimer’s Platform
  - ICARES for aducanumab

- Pre-clinical trial to prevent AD using BAN2401 amyloid monoclonal antibody treatment
Future Rx Strategies

- Anti-amyloid strategies
- Tau interventions
- Anti-inflammatory strategies
- Combined drug treatments
- Gene therapy