Unmet Needs in Neurodegeneration: Focus on Endpoints

2013 CAMD Annual Meeting
October 12, 2013
Bethesda, MD

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CAMD CONFIDENTIAL
Disclosures

• Research Support
  – JAI
  – Pfizer
  – Eisai
  – Lilly
  – NIH
  – Alzheimer’s Association
• Consultant
  – Athena Diagnostics
• Royalties
  – Psychological Assessment Resources
    • Neuropsychological Assessment Battery (NAB)
    • Boston Qualitative Scores System (BQSS) for the Rey Osterrieth Complex Figure
  – Visual Analog Mood Scales (VAMS)
The ADAS-Cog is History

The Old Stuff just isn’t appropriate
  - It is likely that clinical trials for MCI or preclinical AD will not succeed simply because of the wrong outcome measures

Patient Report Outcomes may be inappropriate for MCI or early AD Dementia clinical Trials

What is “functional decline” in MCI and early AD Dementia and how can we measure it?

A composite is only as good as the tests that go into it and the sample from which it is derived
The ADAS-Cog is History

• We are not studying individuals with significant cognitive and functional impairments anymore.

• Even in patients with mild-moderate AD Dementia, the ADAS-Cog was not a great measure.
  – Ceiling effects, skewed distribution
    • Hobart et al., Alz & Dem 2013; Cano et al., JNNP 2010

• Just because a measure is accepted by FDA, doesn’t mean it should be the “Gold Standard” for every study, for every patient group, forever.
Preclinical AD Staging

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ$_{1-42}$

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia

From Sperling et al., 2011
The Old Stuff Just Isn’t Appropriate!

- ADAS-Cog
- MMSE
- CDR
- NTB
- FAQ
- ADCS--ADL
- QoL-AD
- WMS-R Logical Memory
- Etc.
Goal for Appropriate Measure of Episodic Memory

- Highly sensitive to early change.
- Excellent normative data to determine meaningful change and to correct for age, education, gender, and ethnicity.
- Minimal floor or ceiling effects.
- NOT a story recall test
  - List learning tests not impacted by executive dysfunction as much and less likely to have practice effects
Goal for Appropriate Measure of Episodic Memory (cont)

- Brief administration time
- Equivalent Forms
- Lack of complexity of administration/scoring
- Highly standardized administration and scoring procedures
- Possibility of Computerized administration and scoring
- Multiple Languages with appropriate cultural/linguistic and normative consistency
Goal for Appropriate Measure of Episodic Memory (cont)

• Excellent psychometric properties
  – Validity
    • It must test what it is supposed to test.
    • Just because a test is called a “memory” test, doesn’t mean it is actually testing the type of memory functioning impacted by hippocampal degeneration.
Goal for Appropriate Measure of Episodic Memory (cont)

- Excellent psychometric properties (cont)
  - Reliability
    - Test-retest Reliability
    - Alternate-Form Reliability
    - Internal Consistency
    - Limited Practice Effects!
Practice Effects
Comparison between NAB List Learning Delay and WMS-R Logical Memory Delay in Normal Controls over repeated annual administrations at BU ADC

![Graph showing practice effects over number of presentations. The graph compares NC-List Learning and NC-LM-II z-score changes from baseline.](image-url)
Patient Report Outcomes may be inappropriate for MCI or early AD Dementia clinical Trials

- Subjective complaint may predate objective change on neuropsychological measures.
- But....
Patient Reported Outcome Measurement

 Issues with Self Report of Cognitive Concern

• Over-reporting in the “worried well.”
  – Cognitive Complaint Index (ADNI)
• Under-reporting due to belief that it is “normal” to have cognitive impairments or “senior moments.”
• Biggest Issue: As underlying disease worsens, so does the growing lack of awareness of having any problems due to “anosognosia.”
  – the neurologically based inability to be aware that one has a neurological problem
The Anosognosia Problem

<table>
<thead>
<tr>
<th>Functioning</th>
<th>Preclinical</th>
<th>Early MCI</th>
<th>Late MCI</th>
<th>Early Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complaints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graph showing the progression of function and complaints from preclinical to early dementia stages.
Figure adapted from Jack et al. 2010
Sperling et al Alzheimer & Dementia 2011
Issues with **Informant** Report of Cognitive Concern

- No informant available for prevention studies
- Poor informant (lack of contact, impaired, etc.)
- Secondary gain or other reasons to diminish or exaggerate problems
  - Marital or family discord
  - Denial
  - Afraid of confrontation or decreasing independence
What is “functional decline” in MCI and early AD Dementia?

• What is the threshold for considering something as having an impact on independence?
  – “Mild”…. “Significant”

• What aspect of life? – Work, Housework, Finances, Hobbies?

• What are “instrumental activities of living?”
  – Using a telephone, paying taxes, cooking, driving, using a computer

• Once again, there may be a difference between self- and informant-report

• There may be a difference between someone with lots of responsibility and daily challenges versus someone who stays at home without responsibility.
“The vet says I need a hobby. I thought eating and sleeping were my hobbies!”
Performance-Based Measures of Daily Functioning
Performance-Based Measures of Daily Functioning

• Not meant to replace an appropriate measure of “actual” functioning.
• Objective measurement
• Face validity
• Ecological validity
• Examples from Neuropsychological Assessment Battery (NAB)
Edison Electric Company

Statement

Harold Evanston
1406 Chestnut Road, Apt. #64
Germantown, MD 20876

Account Number: 661-837-1842 002
Bill Period: January 16 - February 16

Account Summary:     Amount     Total

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Balance</td>
<td>$50.83</td>
</tr>
<tr>
<td>Payment Received (1/23)</td>
<td>$50.83</td>
</tr>
<tr>
<td>Balance as of January 23</td>
<td>$0</td>
</tr>
<tr>
<td>New Charges</td>
<td>$67.29</td>
</tr>
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</table>

Total Amount Due:  

<table>
<thead>
<tr>
<th>Date of Statement</th>
<th>Payment Due Date</th>
<th>Total Amount Due</th>
</tr>
</thead>
</table>
| February 16       | March 2          | $67.29

Payment Instructions:
Please make check payable to Edison Electric Company.
Please include your account number on the check. Send payment to: Edison Electric Company, 4000 Medway Street, Dennis, MD 21986-4600.
<table>
<thead>
<tr>
<th>Check No.</th>
<th>Date</th>
<th>Transaction Description</th>
<th>Subtraction</th>
<th>Addition</th>
<th>Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1098</td>
<td>1/21</td>
<td>1-800-Bouquet</td>
<td>$17.42</td>
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<td>$113.99</td>
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<tr>
<td>1099</td>
<td>1/25</td>
<td>Nick's Barber Shop</td>
<td>$24.73</td>
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<td>$89.26</td>
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<tr>
<td>1100</td>
<td>2/7</td>
<td>Nippon Restaurant</td>
<td>$46.29</td>
<td></td>
<td>$42.97</td>
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<tr>
<td></td>
<td>2/8</td>
<td>Deposit</td>
<td></td>
<td>$350.00</td>
<td>$392.97</td>
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<td>2/11</td>
<td>Sleepy Mattresses</td>
<td>$275.68</td>
<td></td>
<td>$117.29</td>
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<tr>
<td>1102</td>
<td>2/16</td>
<td>Maryland Municipal Court</td>
<td>$40.00</td>
<td></td>
<td>$77.29</td>
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</table>

Harold Evanston  
3409 Chestnut Road, Apt. #54  
Greenstown, MD 20976  

Date: February 23  

Pay to the Order of ___________________________  

Memo: ___________________________  

Harold Evanston  

No. 1103  

$  

Dollars
• Take one yellow pill two times a day with food.

• Take two green capsules before bed.
First Medication Instruction

- Take one green pill twice a day with food.
- Take one yellow capsule two times a day with food.
- Take one yellow pill two times a day with food.
- Take two yellow pills two times a day with food.

Second Medication Instruction

- Take two green pills before bed.
- Take two green capsules before bed.
- Take two yellow capsules before bed.
- Take one green capsule before bed.
Diana Rivera
31 Stedman Court
Pottersville

474-2569
<table>
<thead>
<tr>
<th>First Name</th>
<th>Last Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julie</td>
<td>Riley</td>
</tr>
<tr>
<td>Diana</td>
<td>Garcia</td>
</tr>
<tr>
<td>Rebecca</td>
<td>Davies</td>
</tr>
<tr>
<td>Delores</td>
<td>Rivera</td>
</tr>
<tr>
<td>Street Number</td>
<td>Street Name</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>38 91</td>
<td>Summit Stedman</td>
</tr>
<tr>
<td>13 31</td>
<td>Caswell Maple</td>
</tr>
<tr>
<td>Court</td>
<td>Way</td>
</tr>
<tr>
<td>Trail</td>
<td>Lane</td>
</tr>
</tbody>
</table>
On Highway 60, travel east. What would your location be if you entered Highway 260 heading south, got off at the third exit, and traveled 2 miles north?
## Questionnaire Title

### Administration Instructions

Say, I am going to ask you a few questions. I want you to answer each question as fully as possible. Questions may be repeated up to three times at examiner's request. If response is very brief or includes only a general concept (e.g., "For safety," "For health," or "It's dangerous") with no specific reference to the question, query by saying, Tell me more.

### Questions With Scoring Criteria

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Why should you blow out candles before going to bed?</td>
<td>2 points: Addresses potential danger of fire. 1 point: No clear response or response is not clear.</td>
<td>2.0</td>
</tr>
<tr>
<td>2. Why should you not leave a young child alone at home?</td>
<td>2 points: Addresses potential danger of choking.</td>
<td>2.0</td>
</tr>
<tr>
<td>3. Why should you replace the batteries in a smoke detector regularly?</td>
<td>2 points: Addresses potential danger of fire.</td>
<td>2.0</td>
</tr>
<tr>
<td>4. What should you do if you take too much of a prescription medication?</td>
<td>2 points: Addresses potential danger of overdose.</td>
<td>2.0</td>
</tr>
<tr>
<td>5. Why should you not unplug electrical appliances while your hands are wet?</td>
<td>2 points: Addresses potential danger of electrical shock.</td>
<td>2.0</td>
</tr>
<tr>
<td>6. Are certain foods marked with an expiration date?</td>
<td>2 points: Addresses potential danger of spoilage.</td>
<td>2.0</td>
</tr>
<tr>
<td>7. Why is it important for people to brush their teeth?</td>
<td>2 points: Addresses potential danger of tooth decay.</td>
<td>2.0</td>
</tr>
<tr>
<td>8. Why is it important to tell your doctor all the medications that you are taking?</td>
<td>2 points: Addresses potential danger of drug interactions.</td>
<td>2.0</td>
</tr>
<tr>
<td>9. Why should you wash your hands before eating?</td>
<td>2 points: Addresses potential danger of foodborne illness.</td>
<td>2.0</td>
</tr>
<tr>
<td>10. What does it mean when your doctor says that there is a 25% chance of having serious side effects from a treatment?</td>
<td>2 points: Addresses potential danger of severe side effects.</td>
<td>2.0</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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Composites

- Believed to be an improvement over use of individual tests as primary outcome measures, especially for adaptive trials

- **Goals:**
  - Smaller samples, Greater power, Shorter studies

- **Reality:**
  - Typically derived from NP measures (as well as ADL and CDR) used in MCI/AD samples
  - May not be appropriate for early MCI or Preclinical samples if developed on later stages
  - Composite scores are only as good as the individual NP measures they are derived from
New Composite Study - CTAD 2013

Ropacki, Hendrix, Seichepine & Stern

• Measures with good psychometric properties and from early MCI yielded improved Composite
  – Outperformed Composites based on older measures used in AD Clinical Trials to-date
• Overall MSDR of 0.71 for the Composite
  – Higher than observed for the Composite of ADAS-Cog, MMSE and NTB items in a pooled ADCS & ADNI MCI population of 0.48
  – Higher than observed for best Composite of ADAS-Cog, MMSE and CDR-SB items of 0.54
Summary

• The old measures of cognition and daily functioning used in AD Dementia clinical trials are not appropriate for prodromal, early MCI, and early dementia trials.

• Patient report outcomes sound good in theory, but….

• Performance-based measures of daily functioning may be helpful.

• Composites are great, but…