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• none

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Beyond ADAS-Cog – Lessons Learned and Moving Ahead
Why a Performance Based Assessment of Cognition to Assess Efficacy?

• **Before AChEIs there was Hydergine**¹
  — Approved for “signs and symptoms of ideopathic decline in mental capacity in the elderly”
  — Primary efficacy measure was the Sandoz Clinical Assessment Geriatric (SCAG) – clinician rated multiple domain assessment – mix of cognitive, behavioral, functional items

• **Then (1976) Relatively specific cholinergic deficit found in patients with neuropathologically confirmed Alzheimer’s disease**
  — This narrowed the target population to an entity with specific clinical and pathological features
  — Clinical diagnostic criteria developed to help identify patients with this pathology

• **The most prominent symptoms uniformly observed in patients with plaques and tangles**
  — Impairment in memory and other cognitive functions including expressive and receptive language, praxis and orientation
  — Impairments were relentlessly progressive

Quantitative Assessments of Symptoms are often the Best Measure of Efficacy

• These are almost always meaningful provided:
  – They measure symptoms that clinicians and patients find important
  – They are readily observable

• Examples:
  – Pain (e.g. WOMAC)
  – Motor problems (e.g. UPDRS)
  – Psychosis (e.g. BPRS)

• Limitations:
  – Not useful for treatment with no acute symptomatic benefit (e.g. antihypertensives, cholesterol or cancer medicines)
  – Threshold for benefit/risk may be hard to define
Efficacy Can Also be Assessed by Time and Frequency of Clinical Events

• **Avoidance of clinically meaningful events is often the therapeutic goal**
  - Readily identifiable
  - Do not happen to all patients – more common in high risk

• **Examples include:**
  - Heart attack
  - Fracture
  - Death

• **Limitations:**
  - Patients & clinicians see no immediate benefit
  - Requires conversion to metric such as RR or NNT
  - Data to determine RR or NNT may be extensive
  - Not all events of equal severity
Special Issues in Efficacy Assessment for a Disorder of Cognition

• **Cognitive Deficit - The defining symptom**
  − Not observable without testing under controlled conditions
  − Translation of test scores to daily experience of patient, family and clinician not obvious
  − Overly sensitive tests could detect treatment effects that are not meaningful

• **Global Clinical Evaluation – The usual clinical standard**
  − Requires both testing and interview
  − Difficult to anchor in long studies

• **Functional Deficit – The most meaningful but problematic**
  − Usually not observable in clinical setting
  − Patients are often poor at self reports
  − Informants are better but reports are often unreliable and difficult to standardize
  − Usual activities vary by culture, gender, age
Hybrid Approach to Efficacy – It Continues to Evolve as Data Accumulates

• 1990 FDA Draft Guidance – The “Co-Primary” Outcome Requirement
To gain an antidementia indication for a product, a sponsor must provide substantial evidence that the product:
  1) has a clinically meaningful effect and
  2) exerts its effect on the 'core' manifestations of dementia.¹

• Modification by EMEA Guidance – 2008
Improvement in symptoms should be assessed in the following three domains:
  1) cognition, as measured by objective tests (cognitive endpoint);
  2) activities of daily living (functional endpoint)
  3) overall clinical response, as reflected by global assessment (global endpoint).²

• Further FDA Modification Proposed in 2013 for MCI and preclinical AD
  1) Possible accelerated approval based on cognitive improvement alone in preclinical AD
  2) Possible approval based on single composite measuring cognition and function³

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# Alzheimer’s Disease Assessment Scale – Cognitive (ADAS-Cog)

<table>
<thead>
<tr>
<th>Category</th>
<th>Items</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>3 items</td>
<td>27 pts.</td>
</tr>
<tr>
<td>Orientation</td>
<td>1 item</td>
<td>8 pts.</td>
</tr>
<tr>
<td>Language</td>
<td>5 items</td>
<td>25 pts.</td>
</tr>
<tr>
<td>Praxis</td>
<td>2 items</td>
<td>10 pts.</td>
</tr>
</tbody>
</table>

**Total**

11 items 70 pts.

**Additions (1997)**

- Digit Cancellation Measure of Attention 5 pts
- Maze Test of Executive Function 5 pts
- Delayed Recall of Word List 10 pts
We’ve Learned that Cognitive Impairment in AD Progresses in a Relatively Predictable Way: Pooled Longitudinal Data from 3223 Patients in 9 Studies

Note: The posterior probability of the average individual's mean ADAS-cog being in the interval is 90%

Aβ amyloid accumulates in brain years before onset of clinical symptoms – Cognitive deterioration is slow thru MCI and Mild AD

Cognitive Deficit is More Evident in Mild Disease than is Functional Deficit

Fig. 3.—Relationship of dementia score to mean plaque count in 60 aged subjects.

Fig. 4.—Relationship of test score to mean plaque count in 60 aged subjects.

ADL Loss is Predicted by Baseline Cognitive Deficit in Older Persons

Criteria for Loss of Function are Difficult to Operationalize in MCI

Symptomatic Treatment Effects on Cognition Appear Before Effects on Function - Donepezil

Figure Legend: Least squares mean (± SEM) change from baseline in the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point.

Figure 2. Kaplan–Meier survival estimates of time to clinically evident functional decline (by investigator, intent-to-treat population).

How has our Knowledge of Cognitive Change in AD Changed?

• Cognitive decline in AD is relentless and predictable
• Amyloid pathology precedes Clinical Symptoms
• The ADAS-Cog and other measures change slowly in MCI and Mild AD
• In patients with AD pathology, cognitive deficit precedes functional deficit – MCI is the state with cognitive but little/no functional deficit
• Cognitive deficit predicts functional deficit in epidemiological studies
• Functional deficit difficult to quantify in mild disease
• All approved symptomatic treatments for AD improve both cognition and function – but functional benefit is evident only with longer observation
Future Directions, Challenges and Solutions

Future Direction: Focus on disease modification treatments in early AD and/or MCI
- Treatment effect on cognition will develop slowly over time as disease course changes
- Functional change will be harder to observe
- Biomarkers will enable selection of patients based on underlying pathology

Challenges: Do existing data provide confidence that an effect on cognition predicts an effect on function?
- Data show a consistent relationship of cognition and function in AD
- Quantification of the predictive power of cognitive change is difficult
- Time lag between cognitive and functional change varies with stage of disease
- Existing tools (ADAS-Cog, MMSE) not optimized for MCI

Solutions: What additional data will be helpful?
- Longitudinal data with consistent measures
- Modified Cognitive Assessment tools for studies in MCI
- More treatment trials with positive treatment effects