Advances in Alzheimer’s Disease Diagnosis and Research: Wyoming Medical Society Annual Meeting

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Disclosures

Dr. Cummings has provided consultation to Abbott, Acadia, Adamas, Anavex, Astellas, Avanir, BMS, Eisai, EnVivo, ExonHit, Janssen, Forest, GE, Genentech, GSK, Lundbeck, Merck, Neurokos, Novartis, Otsuka, Pfizer, Prana, QR Pharma, Sanofi-Aventis and Takeda pharmaceutical companies.

Dr. Cummings has provided consultation to MedAvante, Neurotrax, and UBC assessment companies.

Dr. Cummings owns the copyright of the Neuropsychiatric Inventory

Dr. Cummings has stock options in QR Pharma, Prana, Neurokos, ADAMAS, Medavante
Alzheimer’s Disease Diagnosis and Research

- Prevalence
- Clinical features and diagnosis
- Pathophysiology
- Biomarkers
- Treatment
AD: A Major Public Health Threat

- 5.5 million cases in US now
- One new case every 70 seconds
- 7th leading cause of death
- $172B in annual costs now
- 10.9 million unpaid caregivers
Growth of Number of US Persons with Alzheimer’s Disease

Millions of US Persons

(Hebert LE et al. Arch Neurol 2003; 60: 1119-1122)
Worldwide Prevalence of Alzheimer’s Disease in 2050: > 100 Million Cases

Brookmeyer R et al, 2007
Cost to US of AD in 2050: $1 Trillion!

Alzheimer’s Assn. Changing the Trajectory of AD, 2010
Alzheimer’s is a Life-Long Process

More Likely
Age, genetics (ApoE 4), hypertension, elevated cholesterol, homocysteine, female sex, head trauma

Less Likely
Education, exercise, mental activity, antioxidants in diet
Clinical Features and Diagnosis

- Insidious onset, slow progression
- Recent memory usually involved first
- Remote memory, language, visuospatial skills gradually impaired
- Motor skills and walking preserved until late in course
- Fatal; 6-15 year time course
Brain Atrophy in Alzheimer’s Disease

Alzheimer’s Disease

Normal
Histopathology of Alzheimer’s Disease

Neuritic Plaque

Neurofibrillary Tangle
Histopathology of Alzheimer’s Disease
Alzheimer’s Disease Involves Many Complex Pathways

- Amyloid Protein
- Plaques and Tangles
- Mitochondrial Disturbances (Energy Failure)
- Loss of Synapses (Connections between Nerve Cells)
- Nerve Cell Loss
Brain Atrophy is Revealed by MRI: Memory Areas (Hippocampus) are Most Severely Affected

Healthy Elderly

Alzheimer’s Disease

Images from M Phillips, Cleveland Clinic
Brain Metabolism (FDG PET) Studies Show a Characteristic Pattern in AD

Alzheimer’s Disease

Frontotemporal Dementia
Brain Amyloid Deposits Can Be Visualized by PET (Av-45 and other ligands)
Biomarkers Have Re-Defined AD

- **Preclinical AD (AD pathology)**
  - Normal cognition
  - Positive amyloid imaging, abnormal CSF

- **Prodromal AD (MCI of AD type)**
  - Declining cognition
  - Biomarkers abnormal
  - Do not meet criteria for dementia

- **Alzheimer’s dementia**
  - Dementia
  - Biomarkers indicative of Alzheimer’s disease
Cholinesterase Inhibitor Treatment of Alzheimer’s Disease

- Almost 20 year’s experience (1993 -> now)
- Modest improvement in 25% (2-4 points on ADAS-cog)
- Delayed decline in 80% (6-9 months)
- Multiple domains respond
  - Cognition
  - Activities of daily living
  - Behavior
  - Global
Cholinesterase Inhibitor Treatment of Alzheimer’s Disease

- Effects similar with all agents
- Effect demonstrable in late disease; benefit of therapy is likely persistent throughout the course
- No proven effect on underlying disease
Cholinesterase Inhibitor Treatment of Alzheimer’s Disease

- Gastrointestinal side effects common
  - Diarrhea, nausea, vomiting, anorexia
  - Occur in approximately 15%
- Bradycardia is a contraindication
Cholinesterase Inhibitors

- **Donepezil (Aricept; Aricet)**
  - Mild, moderate, severe AD
  - 5, 10, 23 mg
  - Tablet and orally disintegrating tablet (ODT)

- **Rivastigmine (Exelon)**
  - Mild, moderate AD
  - Mild, moderate Parkinson’s disease dementia
  - 4.6 mg, 9.5 mg patch

- **Galantamine (Razadyne)**
  - Mild, moderate AD
  - 6, 8, 12 mg BID
  - 12, 24 mg extended release formulation
Aricept 23 mg: Severe Impairment Battery

From a 24-week, global, double-blind clinical study (CT.gov identifier NCT00478205) of Aricept 23 mg/day vs Aricept 10 mg/day in 1434 patients with moderate to severe AD.

Please see full prescribing and patient information available at this presentation.
NMDA Receptor Antagonist

- Memantine (Namaeda, Ibixa, Axura)
  - Moderate-severe AD
    - Defined as up to MMSE of 20 in Europe
    - 5, 10, 15, 20 mg weekly titration to 10 mg BID
- Side effects
  - Somnolence, headache, dizziness
- Combination therapy
  - Safe, tolerable, common
Medical Foods

- Generally recognized as safe (GRAS) by FDA
- Treat a metabolic condition
- Available by prescription
- No demonstration of clinical benefit required
Medical Foods

- **CerefolinNAC**
  - B6, B12, folate combination
  - For hyperhomocysteinemia

- **Axona**
  - Caprylic triglyceride—a proprietary formulation of medium-chain triglycerides
  - MCTs increase plasma concentrations of ketone bodies (predominantly β-hydroxybutyrate)
  - Considered an energy source for neurons
Axona® Clinical Study in Mild to Moderate Alzheimer’s Disease (AD)¹

(All Patients)

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale.

Error bars = standard error of the mean (SEM).

Axona® Clinical Study in Mild to Moderate Alzheimer’s Disease¹

ApoE-4 Non-Carriers

ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive subscale; APOE = Apolipoprotein E.

Error bars = standard error of the mean (SEM).

Psychotropics in AD/Dementia

- None approved by FDA for any behavioral indication
- Black box warning on all antipsychotics (atypical and conventional)
  - Increased risk of death (2.5 -> 4.6%)
  - Increased risk of stroke with some
  - Data suggest increasing risk of death with longer exposures
  - Causes of death were cardiovascular and pulmonary
Antipsychotics in Alzheimer’s Disease

- **Motor disturbances**
  - Early onset – parkinsonism
  - Late onset – tardive dyskinesia
  - More common with conventional than atypical agents
- **Cognitive impairment**
- **Stroke**
- **Death**
Antipsychotics Impair Cognition IN Dementia: ADAS-Cog Results (CATIE)
Antipsychotics in AD/Dementia

- Efficacy demonstrated
  - Agitation
  - Psychosis
- Best management option in some circumstances
- Minimize use
- Minimize dose and duration of therapy
- Inform caregiver of risks
- Monitor for side effects
- Balance potential for benefit and harm
Antidepressants in Alzheimer’s Disease

- Commonly used in AD
- None approved by FA for depression of AD
- Several studies show no drug-placebo difference across drug classes
- Possible targets
  - Depression
  - Agitation
  - Anxiety
  - Sleep disturbances
Other Psychotropics in Alzheimer’s Disease

- **Anxiolytics**
  - Short term use for agitation (e.g., lorazepam)
  - Can increase confusion
  - Can increase falls

- **Hypnotics**
  - Sleep disturbances common in AD
  - Anti-depressant
  - Non-benzodiazepine agents (e.g., zolpidem)
Supplements

- Very widely used
- No/limited supportive placebo-controlled data
- Epidemiologic data suggesting preventive benefit of antioxidants
- Little evidence of harm
  - High dose (>400 IU/d) vitamin E may be associated with cardiovascular events
- Consider benefit/harm balance
Non-Pharmacologic Interventions

- For patients
  - Cognitive exercises
  - CG training for behavioral disturbances
- For caregivers
  - Education
  - Support groups
  - Respite
- Limited rigorously controlled data
- Consider benefit/harm ratio
## Cognitive Enhancers in Non-AD Dementias

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular dementia</td>
<td>ChE-Is (off label)</td>
</tr>
<tr>
<td>Parkinson’s disease with dementia</td>
<td>Rivastigmine (FDA approved)</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>ChE-Is (off label)</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Memantine (off label)</td>
</tr>
<tr>
<td>Prion diseases</td>
<td>None</td>
</tr>
</tbody>
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ChE-Is – cholinesterase inhibitors
Dextromethorphan/Quinidine (Nuedexta™)

- Dextromethorphan (NMDA receptor antagonist; sigma receptor agonist) + quinidine (CYP 2D6 inhibitor)
- FDA approved for pseudobulbar affect (PBA)
- Reduced episode counts and scale scores in ALS and MS
- Improved quality of life and quality of relationship scores
Dextromethorphan / Quinidine (Nuedexta): Approved for Pseudobulbar Affect (PBA)

Anti-Alzheimer Treatments in Clinical Trials

- Roughly 100 anti-dementia drugs in clinical trials
- 4 general classes
  - Transmitter-based
  - Anti-amyloid and tau-related protein focused
  - Cell metabolism – PPAR gamma agents, dimebon, anti-oxidants
  - Regeneration – growth factors, stem cells
- Minimum 3-5 years before any new therapies will be available, possibly longer
Ganenterumab Removes Amyloid Protein from the Alzheimer Brain

Before

Slight Increase in Placebo Group

After

(Ostrowitzki S et al. Arch Neurol 2011; ahead of print)
Ganenterumab Removes Amyloid Protein from the Alzheimer Brain

Marked Reduction In Treatment Group

Before

After

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Marked Reduction In Treatment Group

(Ostrowitzki S et al. Arch Neurol 2011; ahead of print)
Comprehensive Integrated Care

- Clinical Trials
- Cog Enhancers
- Behave Pharm
- Pharm Asst’ed Disorders
- Medical Foods
- Diet; Supplement
- Non-Pharm Tx
- Cog Exercise
- Physical Exercise
- CG Care
Alzheimer’s Disease Diagnosis and Research

- Prevalence of AD is high and rising
- Memory loss progresses to death
- Complex interplay of amyloid, tau, other factors
- Biomarkers allow early diagnosis
- Current treatments are symptomatic; most trials involved disease-modifying agents