Update on Dementia and Future Directions

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Disclosure

I have no financial relationships to disclose.
"I'd like to help you, sir, but we only sell extra memory for computers."

93-year-old man to run ING NYC Marathon for 13th time

Jon Mendes
Objectives

• Review Alzheimer’s Disease (AD) and other Dementias

• Review current medications (effectiveness, benefits and risks) used for mild-moderate AD

• Review current medications (effectiveness, benefits and risks) used for moderate to severe AD

• Examine future medications currently being reviewed by the FDA and clinical trials available for AD patients
The Aging Population

Projected U.S. Population by Age and Sex: 2030
(in thousands)

Source: Population Division, U.S. Census Bureau
Released: August 14, 2008
The Aging Population

Projected U.S. Population by Age and Sex: 2050
(in thousands)

Source: Population Division, U.S. Census Bureau
Released: August 14, 2008
Risk Factors for AD and Dementia

• Age is the strongest risk factor for dementia
  – In one study, annual incidence of 0.6% for people 65-69; 1.0% for people 70-74; 2.0% for people 75-79; 3.3% for people 80-84; 8.4% for those >85*
  – Incidence continues to increase with age after 85.
  – Relative uncommon in the younger patient
    • 4.2 cases per 100000 person years among individuals aged 45-64 years*
Risk Factors for AD and dementia

- Family History can be a risk factor for development of AD
  - Patients with a **first-degree relative** of dementia have a 10-30 percent increased risk of developing the disorder*
  - First-degree relatives of African Americans with AD appear to have a higher cumulative risk of dementia than relatives of Caucasians.
  - Presinilin/APP genes for early onset
Race/Ethnic Differences

Figure 13: Proportion of People Aged 65 and Older with Alzheimer’s Disease and Other Dementias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006, N=2,162

Created from data from Gurland et al.\textsuperscript{23}
MCI Has Increased Risk for Dementia

1-2% per year

10-15% per year
AD/DEMENTIA & STAGES
Memory Complaints of Healthy Elderly

Percentage of Elderly

- Recalling names/words 83%
- Recalling where you put things 55%
- Knowing you have told someone something 49%
- Forgetting a task after starting it 41%
- Losing the thread of conversation 40%

Boller et al., Arch Neurol 1991
Presentations of Memory Change

• “Normal” memory change in healthy aging

• Mild Cognitive Impairment (MCI)

• Dementia
  – 4th leading cause of disability, but 2nd most feared
Memory Storage and Retrieval
“Age-Related Decline”

- Mild Brain Atrophy
- Increased white matter abnormality
  - Significance unknown
- Decreased hemodynamic response on functional MRI
- Reduced synaptic density on examination of brain tissue
“Age-Related Decline”

- Leads to declines in:
  - Information processing speed
  - Executive function
  - Learning efficiency
  - Effortful retrieval

Hedden & Gabrieli 2004, Nat Rev.
Normal Aging

Mild Cognitive Impairment (MCI)

- Memory improves
- Memory Stable
- Dementia
What is Mild Cognitive Impairment (MCI)?

- Subjective memory complaint
- Objective memory impairment for age and education
- Largely intact general cognitive function
- Preserved “Activities of Daily Living” (ADLs)

Petersen et al., 1999
Mayo Clinic
Activities of Daily Living (ADLs)

Primary
• Eating
• Dressing
• Ambulating
• Hygiene and Grooming
• Toileting
• Personal devices- hearing aids, glasses.

Secondary
• Shopping
• Cooking
• Housekeeping
• Finances
• Transportation
What causes MCI?

- Depression
  - Memory function may improve with treatment of depression

- Medical Illness (e.g. Hypothyroidism)*
  - Memory function may improve if corrected

- Traumatic injury (e.g. Head injury)*
  - Memory function often stabilizes after a period of recovery

- Vascular disease (e.g. Stroke)*
  - Memory function may stabilize or progress

- Degenerative processes (e.g. Alzheimer’s disease)*
  - Memory function declines over time

* More likely to lead to Dementia
Memory improves
Dementia
Memory Stable
Mild Cognitive Impairment (MCI)
Normal Aging
Memory improves
What is Dementia?

• Memory impairment greater than expected for age **PLUS**

• Impairment in at least one other cognitive ability area

• Difficulty managing Activities of Daily Living
The 5 Cognitive Domains

Memory
Language
Visual-spatial relations
Problem solving
Attention
Dementia - Causes

- Alzheimer’s
- Lewy Body
- Parkinson’s
- Vascular
- Huntington’s Disease
- FrontoTemporal
- Other Neurodegenerative Diseases
- Prion Diseases
- Infectious (HIV, Syphilis)
- Psychiatric
- Medical Diseases/medications
- Normal Pressure Hydrocephalus
- Nutritional
- Alcohol
What is Alzheimer’s disease?

- The most common cause of dementia
  - 75% of dementia cases

- A degenerative disorder of the brain, with memory loss as its hallmark.

- Affects 5.3 million people in the USA

- Increases with age:
  - 1% at 65
  - 4% at 75
  - 24% at 85

1901, Mrs. Auguste Deytch
Beta-amyloid Plaques

Amyloid precursor protein (APP) helps neurons grow and survive.

1. APP sticks through the neuron membrane.
2. Enzymes cut the APP into fragments of protein, including beta-amyloid.
3. Beta-amyloid fragments come together in clumps.

In AD, many of these clumps form, disrupting the work of neurons. This affects the hippocampus (forms memories) and other areas of the brain.
Early AD

Symptoms:
• Short term memory
• Words
• Judgment

Dilemmas:
• Driving
• Finances
Mid AD

Symptoms:
- Behavior
- Dressing
- Insight

Dilemmas:
- Explaining
- Moving
Severe AD

Symptoms:
• Communication
• Mobility
• Swallowing

Dilemmas:
• Risk/benefit
• Nutrition

Lewy Body Dementia
Lewy Body Dementia

- 2nd most common dementia in elderly, 10-15% of cases @ autopsy
  - Central feature: Dementia
    - Fluctuating course, hallucinations, parkinsonism
    - Relative sparing of the memory, compared to attention, executive function, visuo-spatial
Vascular Dementia
Vascular Dementia

• Strategically placed stroke
• Multiple strokes
• Usually thought of as sudden changes
• Only 2% of Dementias in Path Cohort @ UCDavis, pure vascular an etiology
• 30% of Alzheimer’s patients had large strokes
Frontotemporal Dementia
Fronto-Temporal Dementia

• Larger proportion of ‘younger’ dementias
• Classic Pick’s disease
• 3 clinical subtypes
  – Behavioral
  – Semantic (knowledge)
  – Language
• Also associated with Parkinson’s Plus dementias & Lou Gehrig’s disease
Other Dementias

- Pseudodementia
- Dementia w/ Movement Disorders
- Rapidly Progressive Dementia
- Dementia w/ reversible Causes
- Alcohol Dementia, and nutritional deficiencies
- Medical & Psychiatric Illness
EVALUATION
How Do We Make the Diagnosis?

• History & Exam, Neurological & Psychiatric Assessments
• Neuropsychological Testing
• Brain Imaging
• Laboratory Testing (CSF to look for apoE, apoE4 levels?; Genetic testing?)

• Look Carefully for primary Medical & Psychiatric causes
Neuropsych Testing

• MMSE
  – 20-26 mild functional dependence
  – 10-20 moderate levels of dementia, dependence
  – <10 usually severe disease, total dependence
• 1-3 hours usually with a neuropsychologist
• Tests to examine different areas of the brain, cognitively
  – One hundred five patients (50 AD, 38 MCI, 17 subjective complaints) underwent two lumbar punctures, with a mean interval of 21 +/- 9 months. CSF levels of Abeta(1-42), tau, and ptau-181 were measured.
  – Levels of CSF beta-amyloid(1-42) and tau but not phosphorylated tau at threonine 181 increased over time… The cross-sectional difference between diagnostic groups, however, exceeded by far the longitudinal changes within individuals, suggesting that these biomarkers are not sensitive as markers of disease progression.
Structural Imaging: MRI

The Hippocampus Stores and Retrieves our memories
Brain Amyloid Imaging — FDA Approval of Florbetapir F18 Injection

Lucie Yang, M.D., Ph.D., Dwaine Rieves, M.D., and Charles Ganley, M.D.

Florbetapir F18 Scan Usage: Information Summary.

A negative florbetapir scan:
- indicates sparse to no neuritic plaques.
- is inconsistent with a neuropathological diagnosis of Alzheimer’s disease at the time of image acquisition.
- reduces the likelihood that a patient’s cognitive impairment is due to Alzheimer’s disease.

A positive florbetapir scan:
- indicates moderate to frequent amyloid neuritic plaques.
- may be observed in older people with normal cognition and in patients with various neurologic conditions, including Alzheimer’s disease.

Important florbetapir scan limitations:
- A positive scan does not establish a diagnosis of Alzheimer’s disease or other cognitive disorder.
- The scan has not been shown to be useful in predicting the development of dementia or any other neurologic condition, nor has usefulness been shown for monitoring responses to therapies.
Plasma phospholipids identify antecedent memory impairment in older adults

Mark Mapstone¹, Amrita K Cheema²,³, Massimo S Fiandaca⁴,⁵, Xiaogang Zhong⁶, Timothy R Mhyre⁵, Linda H MacArthur⁵, William J Hall⁷, Susan G Fisher⁸,¹⁴, Derick R Peterson⁹, James M Haley¹⁰, Michael D Nazar¹¹, Steven A Rich¹², Dan J Berlau¹³,¹⁴, Carrie B Peltz¹³, Ming T Tan⁶, Claudia H Kawas¹³ & Howard J Federoff⁴,⁵
TREATMENT: NOW AND ON THE HORIZON
Treatments & Prevention?

- Current Medical Treatment
  - Optimize Health: Blood Pressure, Blood Sugars, etc
  - Nonpharmacological methods
  - Treat any concurrent disorder that may be affecting cognition (sleep, depression)
  - Acetylcholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine) & Memantine
  - Supportive care and planning
Non-Pharmacologic Treatments

- Identifying events preceding agitation
- Unmet needs
- Avoiding sudden change in surroundings
- Personal care
- Aromatherapy, music therapy, pet therapy, exercise training
Distinguishing Dementias

• Current Treatments: ACHEi’s & Memantine for AD
  – ACHEi’s may worsen behavior, cognitive symptoms in FTD?.

• Symptommatic Tx:
  – DLB patients more sensitive to antipsychotics
    • Can try Quetiapine, maybe olanzapine first
Cholinesterase inhibitors

- Cholinesterase inhibitors
  - 24 week double blind placebo controlled trial of donepezil in patients with Alzheimer’s
    - Cog function (ADAS-cog) significantly improved at weeks 12, 18, and 24
  - Second study of 565 patients averaged 0.8 MMSE points better
  - Park-Wyllie et al, PLoS Med 2009, did population study in Canada 1.4 million residents data base; found cholinesterase inhibitors had 2 fold increase risk of hospitalization due to bradycardia
  - Tacrine, Donepezil, Rivastigmine, Galantamine
  - Side Effects: cholinergic
  - Used in mild to (how long)?; generally not recommended in MCI
    - Some advocate a trial, and then discontinuation if no benefit
Memantine

- NMDA receptor antagonist “neuroprotective”
- 2003 study, 28 week course of 252 moderate to severe AD pts
  - ADCS-ADL, SIB, CIBIC-Plus, MMSE (0.5 vs 1.2, p 0.18)
- Study involving moderate to severe Alzheimer’s disease (based on Standardized MMSE), had 1.2 points higher on memantine.
- Dizziness/Behavior changes most common side effects.
- Recommended in Mod-Sev, other uses??
Neuropsych Sxs of Dementia

- Agitation, Psychosis, Depression, Sleep
- Nonpharmacologic treatment
- Pharmacologic therapy
  - Antipsychotics, higher mortality, not FDA approved, use with caution (short periods, withdraw if possible, monitor for side effects) – sometimes benefits outweigh risks
  - Cholinesterase inhibitors
  - Antidepressants (limited efficacy, trazodone?)
  - Antiepileptics (limited studies)
  - Benzodiazepines (limited value because of side effects)


**AD and the Brain**

**Beta-amyloid Plaques**

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In AD, many of these clumps form, disrupting the work of neurons. This affects the hippocampus (forms memories) and other areas of the brain.
Current Targets for AD

- Gamma & Beta Secretase
- Tau
- Vaccination & Antibody Strategies
- Nerve Growth Factor
- Mitochondrial stimulation
- 7 phase III trials currently
Tau

• Phase 2 AD trial, 12 month
  – Suggested that 60mg Rember slowed cognitive decline by the ADAS-cog
• Phase 3 in FTD,
• And Phase 3 AD (12 month & 18 month studies) recruiting and underway
Stem Cells & AD

• Neuronal stem cells in AD mouse model
  – Improves cognition
  – Does not change pathology
  – Increase BDNF/Synapse counts
    » Blurton-Jones et al., PNAS 2009

  – Challenges
    • Getting human stem cells
    • Reproducing in long term studies
    • Social impact
    • Side effects

Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

Decision does not affect other Lilly Alzheimer's compounds in development

Promising Alzheimer's drug Gammagard fails key study

Lilly plans another trial of Alzheimer's drug solanezumab
Physical activity slowed Alzheimer’s changes in brains of mice.
-Carl Cotman, UC Irvine, April 2005

The animals that exercised, also learned tasks faster.

In animals that exercised, NEW neurons were seen in the hippocampus
-Fred gage, The Salk Institute, 2004
Nurses’ Health Study
19,000 women, walking

Found higher levels of walking decreased risk of dementia by 20%.
Women walked at an easy pace for at least 90 minutes a week.
JAMA, Sept. 2004
How Much?

• US CDC and AHA-Recommend 30 minutes each day.
• Make sure its OK with your Doctor
Leisure Activity
Albert Einstein Study
500 Seniors for 20 years

Ballroom Dancing Helped Prevent Dementia!
Leisure Activities and the Risk of Dementia in the Elderly

Cognitive Activities:
1. Playing Board games
2. Reading
3. Musical instrument
4. Crossword Puzzles

Physical Activities:
1. Walking
2. Dancing

Points were give for each activity.
All were significantly associated with a reduced risk of dementia.
TREATMENT OF OTHER MEDICAL CONDITIONS
Blood Pressure

- Keeping BP under control prevents:
  - Strokes
  - Heart attacks
  - Kidney failure
  - Dementia
  - ARBs, CCBs
Blood Pressure

- Arterial stiffness seems to correlate to B-amyloid progression and deposition
  - Hughes, et al., JAMA Neurology 2014 E1-E7, published online
A Conceptualized Trajectory of Vascular Factors Related to Arterial Stiffness and β-Amyloid Deposition in the Brain Across Adulthood

Figure represents the proposed relationships between factors related to arterial stiffness and age. Arterial stiffness is measured by blood pressure and pulse wave velocity. Joas et al and others show that blood pressure begins to decline late in life, at least partly explaining why midlife blood pressure is a risk factor for dementia and late-life measures are not. In contrast, pulse wave velocity, a surrogate measure for arterial stiffness, does not appear to decline in late life and continues to increase with age. A recent prospective study of β-amyloid deposition suggests that its progression occurs in a protracted manner over several decades before the diagnosis of dementia. Interestingly, these data also suggest that the rate of β-amyloid deposition slows and may level off as
Lowering BP reduced risk of dementia by 55%

1. High BP increases risk of stroke

2. High BP puts extra stress on arteries carrying oxygen to the brain

3. What about too low BP……..
Insulin Resistance
Diabetes Mellitus

• NIH Study 2004

• Reported a 65% increase risk of AD in those who had Diabetes.

• Netherlands 1999, Diabetes doubles the risk of dementia.
Women and Estrogen

- Menopause and memory loss – Is there a connection?
- Women’s Health Initiative Trial, 2002
  - Used estrogen plus progestin, stopped early due to increased risk of breast cancer, heart disease, stroke and blood clots.
- No change in memory function
- Other studies suggest there may a Critical Window to use hormone replacement
Men and Testosterone

• 2004 research results indicated that older men with lower levels of testosterone may be at higher risk of developing AD.

• In AD men, testosterone levels were $\frac{1}{2}$ the levels of men without AD.
Hormones Replacement
Men and Women

• Neither estrogen for women nor testosterone for men is recommended in dementia prevention at this time.

• Testosterone replacement is indicated for men with low hormone levels.

• Further studies are needed.
Nutrition?
Dietary Recommendations

• No good randomized clinical trials re: diets thus far

• Observational studies
  – suggest fruits and vegetables maybe beneficial
  – Saturated Fats & Fatty Acids maybe associated with cognitive decline
  – Omega 3s, Polyunsaturated Fatty Acids (DHA &EHA Fish oils) may be associated with lower rates of dementia. Highest amount in salmon
Omega-3 Fatty Acids: EPA and DHA

• Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA*) – Both are polyunsaturated fatty acids.
• DHA is in all baby formula – good for brain development.
• DHA is lower in brains of patients with AD
• High Blood DHA level is associated with a reduction in the risk of developing dementia
  and
• A 50% reduction in the risk of AD was associated with the consumption of more than 2 servings of fish per week. Framingham Goup, Archives of Neurology, 2006
Incidence of dementia in subjects with baseline blood DHA levels in the upper quartile compared with those with levels in the lower 3 quartiles.

Omega-3 Fatty Acids

These supplements can be dangerous in some instances. Those with health problems requiring anti-coagulants, i.e. coumadin, diabetics, and other health problems need to check with M.D.
Antioxidants
Antioxidants

• Data is conflicting re: most antioxidants (vit C, beta carotene)

• Some of the observational studies show benefit may stem from food, and not supplemental form

• Vitamin E
  – study in 1999 showed possible delay in dementia; however has had difficulty being reproduced
  – Avoid high doses, if one has cardiovascular disease
  – Recent study coming out again with claim in improvement of ADLs
(Supplement)al intake?
Dietary Supplements and Other

• Homocysteine Reduction
  – B12, B6, Folate usually if deficient in
• Ginko Biloba
• Alcohol
• NSAIDS
• Caffeine?
• Smoking?
Education:

- National Institute of Aging: Formal education may provide a Cognitive Reserve that can reduce effect of AD brain abnormalities (Religious Order Study, 900 priests, nuns, clergy, Rush Presbyterian Hospital).

Greater formal education correlated with better memory and learning ability in older age.
Education Seems to Improve Brain Adaptability

• Frequent cognitive activity corresponded to significant AD risk reductions.

• Also, slower declines in working memory, perceptual speed, episodic memory.
To Avoid Dementia

Use it or lose it!
Staying Active to Stay Active

93-year-old man to run ING NYC Marathon for 13th time

What was his name?
Staying Active to Stay Active

93-year-old man to run ING NYC Marathon for 13th time

Sunday, November 03, 2013

Jon Mendes
Summary

• Memory decline constitutes a spectrum during the aging process
• Diagnosis and treatment are challenges, as well as socioeconomical impact
• For treatment we have two types of medications that help with the symptoms in Alzheimer’s
• Exercise (physical & cognitive), leisure activity, social networks, education may have benefits
• Healthy, balanced diet may have benefits
• Many Drug Trials are currently being conducted.
Resources

• 24/7 Helpline
• Care Consultation
• Family Orientation
• Programs for family caregivers and persons with early and moderate memory loss
• Support Groups
• Medic Alert® + Safe Return®
• Education programs for families and professionals
• Memories in the Making
• Interfaith Services
• Savvy Caregiver Program

Call 1.800.272.3900, 24/7.
• Visit www.alz.org/oc.
Resources

Adult Day Health Care:

**Acacia Adult Day Services**
11391 Acacia Parkway
Garden Grove, CA 92840
Telephone: 714-530-1566 Fax: 714-530-1592

**Irvine Adult Day Health Services (contact Jill Upton)**
20 Lake Road
Irvine, CA 92604
Phone: 949-262-1123 Fax: 949-551-0841

**Alzheimer’s Family Services Center**
9451 Indianapolis Avenue
Huntington Beach, CA 92646
Phone: 714-593-9630 Fax: 714-593-9632
Resources

Elder/Dependent Adult
Elder and Dependent Adult Abuse Reporting - Call 800-451-5155 (24-hour hotline)

• After the report a social worker will respond immediately in an emergency or within 10 calendar days of the report.
• Names of reporting parties are confidential and will not be revealed to the victim, their family or the alleged abuser.
• Elder and Dependent Adult Home Page - Further describes population served and eligibility
• Why Report? - Explains why reporting is important and how it can assist the victim
• Definitions - Explains the different categories of elder and dependent adult abuse
• Making a Report - Phone numbers to call; link to the Long Term Care Ombudsman's website
• Mandated Reporters (those required by law to report elder and dependent adult abuse) - Explains who mandated reporters are, gives step by step mandated reporting, and has link to State of California required abuse form for mandated reporters.
• Confidentiality - Explains reporter's name is confidential
• After the Report - Describes what happens after a report is made
• Related Resources - Other resources for elder and disabled persons
Resources

More Services for Elders and Persons with Disabilities:

**Council on Aging** 714-479-0107  
Office of the Long-term Care Ombudsman, Health Insurance Counseling and Advocacy Program (HICAP), Financial Abuse Specialist Team (FAST).

**Dayle McIntosh Center** 714-621-3300  
Provides services and advocacy for persons with disabilities.

**Legal Aid** 714-571-5200  
Senior Advocacy - provides free legal services to people at or below the poverty level who are age 60 years or older and live in Orange County.

**Office on Aging** 800-510-2020  
Provides information and assistance for older adults and caregivers.