Decreasing the Impact of Dementia:

The Value of Assessment and Networks

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DISCLOSURE DECLARATION

Dr. Murman has the following financial relationships:

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• Advisory Board
  • Biogen
Learning Objectives:

- Discuss normal cognitive aging, the relationship between aging and dementia, specific causes of dementia, and the impact of dependence on outcomes in patients with dementia.
- List healthy lifestyles associated with successful cognitive aging and treatments for Alzheimer’s disease, including possible future approaches.
- Describe the value of assessments for healthy older adults and those with symptoms of dementia.
- Explain the potential value of dementia registries and practice-based research networks for patients with dementia, caregivers and providers.

Cognition and “Normal” Aging

![Graph showing change in crystallized and fluid abilities over age](image)

Figure 1: Change in “crystallized” cognitive abilities, represented here as vocabulary, and “fluid” cognitive abilities, represented here as processing speed, with age in normal subjects. Graph is based upon data presented by T.A. Salthouse and colleagues. Zero line represents the mean or average performance on these measures, while values above zero represent better than average performance and below the line worse than average performance.

Neuronal Synapses

Synapses, Age, and Health

Healthy  Aging  Disease
Synaptic and Cognitive Reserve

- Synapses are created and strengthen with learning and mentally stimulating activities
- Having more synapses builds redundancy in neuronal connections and creates cognitive reserve
- Synapses are gradually lost with normal aging and much more rapidly with disease
- Greater cognitive reserve delays symptoms onset in the face of neurodegenerative diseases such as Alzheimer’s disease and slows progression

Cognitive Decline with Age and Disease

Figure 2: Change in synaptic density with advancing age in three groups: when synaptic density declines to 80% of maximal density, symptoms of dementia would be expected i.e., dementia threshold level. Cognitive reserve is effective in attenuating this decline and what has been termed “cognitive reserve.” The graph shows how synaptic density drops more rapidly with disease (AD and lower age) as compared to normal aging alone and normal reserve + normal aging. A hypothetically determined “threshold” level of synaptic density was established at 80% of maximal density, beyond which disease symptoms would be expected. 

Murman, Semin Hear 2015; 36:111-21. ‘Dementia Threshold’
Age and Dementia Prevalence

SLIDE 1
Alzheimer’s Disease Doubles in Frequency Every 5 Years After the Age of 60

Types of Dementia

- Dementia is the loss of memory due to changes in the brain
- Alzheimer’s is the most common form
- Many mixed cases
- Many memory disorders are reversible and not truly dementia
Alzheimer’s Disease

- Most common cause of dementia
- Gradual onset, gradual progression
- Memory loss first and most prominent symptom
- No focal findings or gait disorder early
- Genetic causes and genetic risk factors
- Becomes exponentially more common with age
  - 3-5% of population at age 65
  - 30-50% of population at age 85

What Alois Alzheimer’s saw and described in 1906
Evolution of Amyloid and Tau Accumulation in AD

Model of Disease Progression

Healthy Control
Asymptomatic

Preclinical AD
Asymptomatic

Prodromal AD
MCI

Alzheimer’s Disease
Dementia

Aging, MCI, and AD

Cognitive function

Preclinical

Aging

MCI

Dementia

Years
AD Diagnostic “Red Flags”

- Abrupt onset, stroke symptoms
- Rapid progression
- Early gait changes, tremor, parkinsonism
- Early visual hallucinations, disinhibition,
- Early loss of expressive language
- Early myoclonus, seizures

Clinical Features of AD vs VaD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Alzheimer’s Disease</th>
<th>Vascular Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual, insidious</td>
<td>Sudden or gradual</td>
</tr>
<tr>
<td>Progression</td>
<td>Constant</td>
<td>Slow, stepwise</td>
</tr>
<tr>
<td>Focal Signs</td>
<td>Usually absent</td>
<td>Present</td>
</tr>
<tr>
<td>Memory Deficits</td>
<td>Early and severe</td>
<td>Milder, Subcortical</td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td>Late</td>
<td>Early and severe</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Normal, atrophy</td>
<td>Vascular abnormalities</td>
</tr>
</tbody>
</table>
White Matter Lesions

Large Vessel Infarct

Micro-Hemorrhage

Small Vessel Infarct

Lancet 2015; 386:1698-06

Lewy Body Dementia

Visual hallucinations
(early)

Motor dysfunction
(may look like Parkinson's)

Cognitive dysfunction
(may look like Alzheimer's)

Fluctuating levels of attention
(May look like delirium)

Acting out dreams
(REM sleep behavior disorder and/or other sleep disturbances)

Autonomic dysfunction
Importance of “Non-AD” Dementias

- Cerebrovascular disease is preventable
- Dementia with Lewy Body (DLB) patients are at increased risk of adverse medication reactions, delirium, falls, and institutionalization. DLB patients do respond to cholinesterase inhibitors
- Normal Pressure Hydrocephalus is treatable
- Rapidly progressive dementia may represent a treatable autoimmune condition or prion disease
Quality of Life and Dependence

EQ5D-US

Dependence stage

Costs and Dependence Stage

Costs of care, thousands

Total direct cost decomposition

Costs of care, thousands

Very Mild Mild Mild to Moderate Moderate Severe Very Severe

Dependence stage
How do we decrease the impact of dementia?

Factors that Increase or Decrease Risk of Cognitive Decline

Fig. 1. Strength of evidence on risk factors for cognitive decline.

Baumgart et al. 2016 Alzheimer’s & Dementia
Factors that Increase or Decrease Risk of Dementia

- Traumatic Brain Injury
- Mid-Life Obesity
- Mid-Life Hypertension
- Current Smoking
- Diabetes
- History of Depression
- Sleep Disturbances
- Hyperlipidemia

**Dementia**

- Years of Formal Education
- Physical Activity
- Mediterranean Diet
- Cognitive Training
- Moderate Alcohol Consumption
- Social Engagement

**KEY:**
- Strong Evidence
- Moderate Evidence
- Lower Evidence
- Insufficient Evidence

Fig. 2. Strength of evidence on risk factors for dementia.

Baumgart et al. 2016 Alzheimer’s & Dementia

Lifestyle for “Brain Health”

- Exercise Regularly
- Mentally Engaged
- Healthy Diet
- Socially Connected
- Control HTN, Lipids, DM
- Good Sleep
- Avoid Toxins/Head Trauma

Alzheimer’s Association
Lifestyle Focused Trials

- **U.S. Pointer**
  - US study to protect brain health through lifestyle interventions to reduce risk
  - 2-year study of impact of exercise, diet, cognitive and social engagement on cognitive outcomes
  - 5 sites, n=2000 subjects, sedentary, poor diet, no cognitive impairment

- **Exert Trial**
  - AD Cooperative Study (ADCS) group trial
  - 18-month trial comparing aerobic training vs. stretching to slow progression of Mild Cognitive Impairment. Will partner with YMCA at 14 sites.
  - Will evaluate rate of cognitive impairments and functional limitations

FDA-approved Medications for AD

- tacrine - 1993*
- donepezil - 1996*
- rivastigmine - 2000*
- galantamine - 2001*
- memantine – 2003*

*FDA approval date
Amyloid β in AD

Anti-Amyloid β Trials in AD

Secondary prevention in Alzheimer’s disease

Preclinical

A4 Study

“Normal” Aging

Cognition

Dementia

Years

aducanumab
A4 Study Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85, CDR=0), who have evidence of amyloid-β pathology on amyloid PET imaging
- Randomized, double-blind, placebo-controlled trial of solanezumab IV monthly for 4.5 years vs. placebo
- Trial n=1000+ (N=500+ per treatment arm)
- Observational cohort of amyloid negative subjects – LEARN study

A4 Prevention Trial Study Sites

Trial supported by the National Institutes of Health and Eli Lilly Co. and coordinated by the Alzheimer’s Clinical Trials Consortium (ACTC)
Aducanumab for prodromal to mild Alzheimer’s disease

- Monoclonal antibody directed against amyloid β.
- Drug is given as a monthly IV infusion
- One phase 3 trial (Emerge) met all efficacy end points at highest dose and had acceptable safety profile, but second phase 3 trial (Engage) did not. Both were stopped early.
- Important side effect: ARIA (i.e. vasogenic edema and microhemorrhages) common but reversible
- Biogen is seeking FDA approval for this drug for patients with prodromal to mild AD

**EMERGE: Primary and secondary endpoints from final data set at Week 78**

<table>
<thead>
<tr>
<th></th>
<th>Placebo decline (n=548)</th>
<th>Difference vs. placebo (%)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low dose (n=543)</td>
<td>High dose (n=547)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>1.74</td>
<td>-0.26 (-15%)</td>
<td>-0.39 (-22%)</td>
</tr>
<tr>
<td>MMSE</td>
<td>-3.3</td>
<td>-0.1 (-3%)</td>
<td>0.6 (-18%)</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>5.182</td>
<td>-0.701 (-14%)</td>
<td>-1.400 (-27%)</td>
</tr>
<tr>
<td>ADCS-ADL-MCI</td>
<td>-4.3</td>
<td>0.7 (-16%)</td>
<td>1.7 (-40%)</td>
</tr>
</tbody>
</table>

**EMERGE: Longitudinal change from baseline in amyloid PET SUVr**
Other AD Trials at UNMC

- **Graduate II Study**
  - Trial of gantenerumab in prodromal to mild AD
  - Drug is given as subcutaneous injection
  - 2-year study, gantenerumab vs. placebo

- **ADvance II Study**
  - Deep brain stimulation (DBS) for patients with mild AD
  - DBS stimulation is trying to increase activity in the brain’s memory circuits
  - 1-year stimulation vs. sham, then everyone will get DBS stimulation with 3 more years of follow-up

- **Green AD Study**
  - Trial of oligomannate in mild to moderate AD
  - Oral medication that was recently approved in China is proposed to decrease neuroinflammation via its effects on gut microbiome

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Care Ecosystem Trial

*Figure 2. The Care Ecosystem Model*

CTN=Care Team Navigator
Randomized trail of CE vs usual care in 780 patient-caregiver dyads at UCSF and UNMC sites for 12 months. (CE=512, UC=268)

Care Ecosystem program significantly improved patient quality of life as judged by caregiver, significantly decreased caregiver depression and burden, and significantly reduced emergency department visits.

The value of assessments, registries and networks
Primary Care Screening and Management of Cognitive Impairment Symptoms is Vital!

- Location of first contact with the healthcare system for most patients with dementia symptoms
- Can identify and treat conditions worsening dementia symptoms
- Medications are available to help many symptoms of dementia including impairments of cognition and behavioral symptoms
- Can provide education, support, and community resource referrals to help keep patient in home environment longer

Quality Indicators in Ambulatory Dementia Care Project

- Examined 22 quality indicators for ambulatory dementia care based upon expert opinion
  - Data was collected from electronic medical record data and chart review, and mailed caregiver survey
  - Monitored care received for 3 years
- Used the Henry Ford Health System as source of patients and data between 2005 and 2008
  - n=326 with EHR data, n=178 also had survey data
- Funded by grant from Alzheimer’s Association
1. Evaluating Dementia Symptoms

<table>
<thead>
<tr>
<th>Dementia Assessments</th>
<th>% Receiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Diagnosis Made</td>
<td>89</td>
</tr>
<tr>
<td>Lab Test (B12, TSH)</td>
<td>78</td>
</tr>
<tr>
<td>Brain Imaging (CT or MRI)</td>
<td>74</td>
</tr>
<tr>
<td>Annual assessment of cognition</td>
<td>40</td>
</tr>
<tr>
<td>Annual assessment of behavior</td>
<td>39</td>
</tr>
<tr>
<td>Annual assessment of function</td>
<td>46</td>
</tr>
</tbody>
</table>

2. Supporting Patients and Families

<table>
<thead>
<tr>
<th>Psychosocial Interventions</th>
<th>% Receiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education Provided</td>
<td>80</td>
</tr>
<tr>
<td>Referral to Community Resources</td>
<td>62</td>
</tr>
<tr>
<td>Driving Safety Addressed</td>
<td>74</td>
</tr>
<tr>
<td>Alternative Decision Maker Discussed</td>
<td>67</td>
</tr>
<tr>
<td>Advanced Directives Discussed</td>
<td>53</td>
</tr>
</tbody>
</table>
### 3. Medication Use in Dementia Care

<table>
<thead>
<tr>
<th>Pharmacologic Treatment</th>
<th>% Receiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase Inhibitor Prescribed</td>
<td>91</td>
</tr>
<tr>
<td>Persistent Use of Cholinesterase Inhibitor</td>
<td>35</td>
</tr>
<tr>
<td>Memantine for Mod. to Severe AD</td>
<td>52</td>
</tr>
<tr>
<td>Medication Used for Severe Psychiatric Symptoms</td>
<td>57</td>
</tr>
<tr>
<td>Anti-Cholinergic Medications Avoided</td>
<td>89</td>
</tr>
</tbody>
</table>

### 4. Managing Co-Morbid Conditions

<table>
<thead>
<tr>
<th>Co-Morbid Disease Mgmt.</th>
<th>% Receiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet Rx (DM, CHD, CVD)</td>
<td>81</td>
</tr>
<tr>
<td>If Diabetes, then yearly HgA1c</td>
<td>87</td>
</tr>
<tr>
<td>If Diabetes, then BS control (A1c&lt;9%)</td>
<td>72</td>
</tr>
<tr>
<td>If Hypertension, then BP control &lt;140/90</td>
<td>63</td>
</tr>
<tr>
<td>If DM, CHD, CVD, then lipid testing</td>
<td>89</td>
</tr>
<tr>
<td>Lipid control (LDL&lt;130), if high risk grp</td>
<td>51</td>
</tr>
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</table>
## Dementia Care Indexes and Outcomes

<table>
<thead>
<tr>
<th>Index Measure</th>
<th>Mean ± Std. Dev.</th>
<th>Correlations with Outcomes</th>
<th>Satisfaction (Health Plan)</th>
<th>2-Year Costs (Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Satisfaction (Health Plan)</td>
<td>2-Year Costs (Log)</td>
</tr>
<tr>
<td>AD-Care IQ Index</td>
<td>69.5 ± 17.4</td>
<td>0.28</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>(percent of 22)</td>
<td></td>
<td>p&lt;0.01</td>
<td>p=0.79</td>
<td></td>
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<tr>
<td>Dementia Core 12</td>
<td>8.3 ± 2.4</td>
<td>0.24</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>(0-12)</td>
<td></td>
<td>p&lt;0.01</td>
<td>p=0.39</td>
<td></td>
</tr>
<tr>
<td>Dementia Core 6</td>
<td>4.5 ± 1.2</td>
<td>0.24</td>
<td>-0.05</td>
<td></td>
</tr>
<tr>
<td>(0-6)</td>
<td></td>
<td>p&lt;0.01</td>
<td>p=0.49</td>
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</table>
Great Plains Cognitive Network (GP CogNET) Grant Goals

- Develop registry of adults (≥50 years old) interested in mild and brain health research that would link survey data and EHR data.
- Build a network of family practice clinics across Nebraska and the Dakotas who are interested in dementia care and research.
  - NE: UNMC clinics, Butler Co. Clinics, Fillmore Co. Clinic and Fontenelle Clinic
  - ND: Sanford Health Bismarck and Fargo
  - SD: Sanford Health Sioux Falls
GP CogNET Registry

- Open to adults 50 and older in NE, SD, ND.
- Can enroll online or complete paper form of questionnaires (self report and/or proxy)
- Data collection is modeled after the National Alzheimer’s Coordinating Center’s (NACC) Uniform Data Set (UDS)
  - Demographics, Dx (self-reported), staging (QDRS), IADL function (FAQ), dependence (DS), psychiatric symptoms (NPI-Q), QoL (EQ-5D), family history
- Linkage with EHR
  - Capture ICD-10 Dx, Co-morbid PMH/PSH, medications prescribed, health care utilization

This is GP CogNET:
Striving to create a dedicated research network for Alzheimer’s disease and related diseases, by linking community members to brain-health focused research, education, and care.
Value of GP CogNET

- The GP CogNET registry provides patients and their families information about research opportunities and educational updates and provides researchers access to potential research subjects.
- The GP CogNET practice-based research network (PBRN) can enhance researcher’s ability to perform community-based research, can provide data for quality improvement projects, and can be used as a platform for education (e.g. Project ECHO).
PARTICIPANTS NEEDED

- Enroll in CogNET Registry
- Join GP CogNET PBRN
- Access feasibility
- Determine what works
- Conduct community-based research

Conclusions

- Age-related declines in cognition can be slowed with a healthy lifestyle.
- There are emerging approaches to decrease the impact of dementia.
- A thorough evaluation is needed for those with symptoms of dementia and ongoing assessments of symptoms are needed to guide high quality disease management.
- The Great Plains Cognitive Network is a potentially valuable resource for patients, families, health care providers and researchers to facilitate research and education to decrease the impact of dementia.
Questions?

- For questions related to this presentation you can contact Dr. Daniel Murman at dlmurman@unmc.edu, 402-559-6591 (academic office), 402-559-8600 (clinic)
### Assessment Tools: Cognition
- Ascertain Dementia 8 Questionnaire
- Mini-Cog
- Mini-Mental State Examination
- Montreal Cognitive Assessment
- Formal Neuropsychological Evaluation

### Assessment Tools: Function
- Functional Activities Questionnaire
- Functional Assessment Staging Tool

### Assessment Tools: Psychiatric
- Geriatric Depression Scale or PDQ-9
- Neuropsychiatric Inventory Questionnaire