Advancing the Prevention & Treatment of Alzheimer’s Disease by 2025
Kathleen A. Welsh-Bohmer PhD
Director, Bryan Alzheimer’s Center at Duke University
DISCLOSURES

- Dr. Welsh-Bohmer is the Neuropsychology Lead for a large 59 site global pharmaceutical company supported clinical trial to delay AD onset, the TOMMORROW study

- Contracts through Takeda and Zinfandel Pharmaceutical Companies

- AD Center support through series of federal grants

  Joseph & Kathleen Bryan Alzheimer’s Disease Research Center (Bryan ADRC): P30 AG028377 P50 AG05128; Cache County Memory Study in Aging (CCMS): R01 AG11380U0; Aging and Dementia Study (ADAMS-HRS): AG09740 & AG027010
Here is Jane. Jane has been noticed some embarrassing problems with her memory for about a year now, ever since she retired and sold her business. She has difficulty tracking conversations and she is now more likely to repeat herself, unsure with whom she may have shared recent updates about her children and grandchildren.
Laboratory tests and even brain imaging studies all are normal. But Jane knows that Alzheimer’s disease runs in her family. She has always been prepared for the possibility that this disease might also affect her one day.
Her family reassures her, pointing out how capable she is in all her activities. Her primary care doctor tells her that her concerns are normal and nothing more than age. Laboratory tests and even brain imaging studies all are normal.
Is that “one day” now here?

Do I have Alzheimer’s disease or is this just what I should expect with normal aging?

What can I do about it?
Alzheimer’s disease (AD) is one of the most dreaded conditions, among the most feared diagnoses for adults over the age of 65

- Recent surveys indicate that 94% of physicians disclose diagnosis of terminal cancer
- Same group of physicians are reluctant to disclose the diagnosis of Alzheimer’s disease to their patients

Blendon RJ. et al  Key Findings from a Five-Country Survey of Public Attitudes about Alzheimer’s Disease. Data from the Harvard School of Public Policy and Alzheimer’s Europe study (2011)
EVERY 70 SECONDS....

ANOTHER CASE OF ALZHEIMERS DISEASE IS DIAGNOSED
By the end of the discussion in one hour.....

50 new cases in this country will have been diagnosed
By the end of next week …..

There will be 4,800 new cases
Currently…..

- 5.2 million people with Alzheimer’s
- 200 billion dollars in annual costs
- 6th leading cause of death
- >15 million unpaid caregivers
Without a cure....

Number of People with Alzheimer’s Disease
Using Current Projections vs. Projections with Delayed Onset and Slowed Progression

13.4 million + Americans affected by 2050

1.1 Trillion annually
(Alz Assoc, 2013)

(Rand Report 2013 NEJM; & Alz & Dementia 2013 9:208-45)
Delaying onset of dementia by 5 years....

8.1 million + Americans affected by 2050

5.3 million fewer Americans

Net decrease of 40%

(Facts and Figures - Alz Association 2013)
Where we are today....

**Bad News**

- There is no treatment that will allow us to prevent the disease from occurring
- There is no treatment to stop the disease once it has started

**Good News**

Considerable progress in:

- Scientific understanding of the biology of the disease
- Advances in technology, allowing earlier diagnosis and treatment possibilities
- Evidence based approaches for lowering risk and promoting healthy cognition
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Alzheimer’s disease ≠ Aging

“Auguste D” - Alzheimer’s Original Case

Admitted to Frankfurt Asylum Nov 26, 1901
- Mistrust of husband and female neighbor
- Mistakes in food preparation; neglected housework; could not find way around apartment; hid objects, then could not find them
- Delusions of harm
- Memory deficits, perseverative, aphasic
- Agitated, screaming, strikes other patients

Died in April 1906; bedridden, decubitus, 74 lbs
Alzheimer Disease:
Amyloid Plaques & Neurofibrillary Tangles

Beta amyloid “plaques”

Atrophy

Neurofibrillary Tangles (p-Tau protein)
Alzheimer’s Disease

- AD is common- affecting 10% over age 65
  It is age-associated and becomes more prevalent with advancing age;
  30-47% over age 85 have the illness
- Characteristic problem is different from normal age-related memory loss
  Characterized by profound forgetfulness for recent events and it benefits very little from reminders
- *Gradual and inexorable*
  Leads to functional disability & always fatal
Tangles....
Under the Microscope

Mild Disease

Moderate Disease

Severe Disease
Alzheimer’s—Chronic disease (3 stages)

Latent Stage ("1º prevention")

Prodromal AD/ Mild cognitive impairment MCI ("2º prevention")

Threshold

Symptomatic Stage
(Treatment)

Age

Normal Cognitive Aging

- Linear decline by age on measures of attention, concentration, rapid visuospatial analysis, episodic memory
- Resistant to age are aspects of decision making and abstraction based on lifetime of acquired knowledge

From Park DC et al 2002, Psychology & Aging, 17, p. 305. Copyright 2002 by the American Psychological Association
Memory Change in Aging ≠ Memory Loss of AD

Chelune & Foster, CCMS 2007
Biomarkers of Alzheimer’s disease

International Working Group (Dubois 2007, Lancet Neurology)
NIA-Alzheimer’s Association (Sperling 2011, Alz Dementia)

- Measure proteins abnormal in AD (amyloid and tau) in cerebrospinal fluid (CSF)
  - or-
- Use new imaging methods — Amyloid Brain imaging using Positron Emission Tomography (PET) imaging
  - Amyloid can be tagged with a radiopharmaceutical (e.g. F18 florbetapir seen here) and can then be visualized on imaging with PET
  - Three different agents now FDA approved for detecting abnormal levels of brain amyloid.

Sperling R et al NeuroMolecular Medicine 2010
Examined the utility of amyloid PET imaging and CSF biomarkers in older adults (n=122) and MCI patients (n=34) who 3 years later develop AD dementia

- Measures of $A\beta_{42}/$total tau and $A\beta_{42}/p$-tau had highest accuracy of the fluid biomarkers - Accurate 93-94%
- Amyloid PET measures had similar level of accuracy – Accurate 92-93%

No improvement by adding the two tests (imaging & CSF) together, suggesting they are equally accurate
Treating & Preventing Alzheimer’s

What is utility of an early diagnosis?

Can we do anything to treat the disease?

Can we prevent progression?
The two major treatment approaches:

- Symptomatic treatment
- Disease-modifying treatment
Cholinesterase Inhibitors (1993-97)

<table>
<thead>
<tr>
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**NEW COMBINED TREATMENT (NAMZARIC) - 2014**

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**CURRENT FDA APPROVED DRUGS FOR AD & THEIR EFFECTS**

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**For donepezil (10 mg/d) versus placebo (Alzheimer disease [AD]), all severity levels), the estimate was statistically significant (P < 0.001) and tests for heterogeneity were not significant (I² = 0.0%; 95% CI: 0.0%–9.9%). For donepezil (10 mg/d) versus placebo (mild cognitive impairment), the estimate was not significant (I² = 50%) and tests for heterogeneity were significant (P = 0.05; 95% CI: 0.0%–95.5%). For donepezil (10 mg/d) versus placebo (mild-to-moderate vascular dementia), the estimate was significant (P < 0.001) and tests for heterogeneity were not significant (I² = 0.0%; 95% CI: 0.0%–94.9%). For rivastigmine (24 mg) versus placebo (mild-to-moderate AD), the estimate was significant (P = 0.05; 95% CI: 0.0%–97.3%). For rivastigmine (24 mg) versus placebo (mild-to-moderate AD and vascular dementia), the estimate was significant (P = 0.001; 95% CI: 0.0%–90.8%). For memantine (20 mg) versus placebo (mild-to-moderate AD), the estimate was not significant (P = 0.05; 95% CI: 0.0%–97.3%). For memantine (20 mg) versus placebo (mild-to-moderate vascular dementia), the estimate was not significant (P = 0.001; 95% CI: 0.0%–90.8%). For memantine (20 mg) versus placebo (mild-to-moderate vascular dementia), the estimate was significant (P < 0.001) and tests for heterogeneity were not significant (I² = 0.0%; 95% CI: 0.0%–90.8%).**
National Alzheimer's Project Act (NAPA)

- January 4, 2011
  - Passed unanimously by both houses of Congress
  - Signed into law by President Obama
- Creates a national strategic plan to address & overcome the escalating crisis of Alzheimer’s disease
- 2013 goal announced to develop treatments to slow progression and prevent onset of AD by 2025
National Alzheimer's Project Act (NAPA)

- Congress added $100 million in 2014 to the National Institute on Aging's portfolio for Alzheimer's research.

- Doubled the $100 million-going to the so-called BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies) – important for new insights into treatment.
National Alzheimer's Project Act (NAPA)

- To fully meet the 2025 goal will require **$2 billion** annually over the next decade in research funding.
- 30 July 2015 - NIH requested an additional $323 million in Alzheimer's disease funding over the $737 million base appropriation. If approved:
  - $36.5 million for development of new biomarkers and disease-monitoring technologies.
  - $92.8 million to go toward translational research and clinical interventions.
  - $45.1 million to studying Alzheimer's disease epidemiology; and
  - $9.8 million to improving how Alzheimer's disease patients are cared for, such as optimizing dosing regimens with existing drugs.
  - $31 million would be used to improve resources for researchers including data and tissue repositories; and
  - $35.4 million to help establish and support research partnerships between the public and private sectors.
  - NIH to submit budget based on professional judgment 2017-2025 to reach milestones of national plan.

*Where's the War on Alzheimer's? As research funding lags, cases are increasing — with staggering costs.* T.R. Reid (www.aarp.org/health/brain-health/info-2015/alzheimers-research.html)
New Novel Approaches
Aiming at Key AD Targets

- Ultrasound treatments in transgenic mice to remove Aβ by allowing brief opening of blood-brain barrier
  (Leinenga & Gotz, Science Transl Med, March 11 2015)

- Yale researchers repurposed a cancer drug (AZD053 Saracatinib) to prevent amyloid fibrils from attaching to neuron cell surface and memory improved on 3 different memory tasks in treated mice
  (Kaufman et al 2015 Annals of Neurology)

- Duke researchers were able to block an abnormal immune cell response in brain with a cancer drug (DMSO) and blocked brain plaques and memory problems in transgenic mice
  (Colton et al 2015 J Neuroscience)
2015 Alzheimer’s Disease Prevention Studies

- Dominantly Inherited Alzheimers Network (DIAN) Trial Unit (DIAN-TU; families with disease),
- Alzheimer’s Prevention Initiative (API) examine compounds to prevent AD onset and cognitive decline in genetic forms of the disease (young age of onset)
- Alzheimer’s Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD (ADCS-A4 Study) will examine treatments in individuals who show increased amyloid accumulation in their brains on amyloid imaging studies
- TOMMORROW Study examines individuals at high and low genetic risk (algorithm: age, APOE, TOMM40)
What can we do now????

▪ Seven things that can be done now to reduce risk of disease and
▪ Potentially have a positive impact on memory decline & dementia progression
Step 1: Change in Mindset

- Not all memory change is disease & many disorders have a treatable component
- Not powerless as we age & have responsibility to maintain health
  - Continued contributions (big or small) to the larger society, family, & friends
  - Older workers/volunteers bring the “Wisdom of age” and a life well-lived to the dynamic
Step 2: Treat what can be treated

▪ Stop smoking
▪ Reduce alcohol consumption
▪ Management of medical conditions:
  ▫ Heart disease & vascular risk conditions
    ▪ Hypertension, diabetes, high cholesterol
  ▫ Thyroid disease
  ▫ Sleep disorders
  ▫ Pain, arthritis
  ▫ Anxiety & depression
Step 3 - Get Physically Active

World Health Organization Guidelines 2011 Global recommendations on physical activity for health

Senior Guidelines For Physical Activity

<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Aerobic Exercise</td>
<td>Older adults need moderate-intensity aerobic physical activity for a minimum of 30 minutes five days each week or vigorous intensity aerobic activity for a minimum of 20 minutes three days a week. (Moderate intensity is when you feel “warm and slightly out of breath,” and vigorous is when you feel “out of breath and sweaty.”)</td>
</tr>
<tr>
<td>Resistance Exercise</td>
<td>Older adults will benefit from performing activities that maintain or increase muscular strength and endurance for a minimum of two days each week. It is recommended that eight to 10 exercises be performed on two or more nonconsecutive days per week using the major muscle groups.</td>
</tr>
<tr>
<td>Flexibility Exercise</td>
<td>To maintain the flexibility necessary for regular physical activity and daily life, older adults should perform activities that maintain or increase flexibility at least two days each week for at least 10 minutes each day.</td>
</tr>
<tr>
<td>Balance Exercise</td>
<td>To reduce risk of injury from falls, older adults with substantial risk of falls (for example, with frequent falls or mobility problems) should perform exercises that maintain or improve balance.</td>
</tr>
</tbody>
</table>
Exercise your Body
The Evidence:

- **Experimental Studies:**
  - Active adult mice have reduced cerebral accumulation of AB plaques and ROS
  - Exercise up-regulates proteins that stimulate neural growth in the hippocampus (learning and memory)
Best Test:
Randomized Exercise Trials

- Meta-analysis of aerobic exercise trials
  - Non-demented adults (MCI included)
  - Literature search of 5,538 articles
  - 29 randomized trials & 2,049 participants

- Aerobic exercise improves cognitive function
  - Attention and processing speed \( (g = 0.158, p = .003) \)
  - Executive function \( (g = 0.123, p = .018) \)
  - Memory \( (g = 0.128, p = .026) \)
  - Working Memory \( (g = 0.032, p = .642) \)

- Improvements larger among MCI

- Findings consistent across samples and training mode
  - Training: intensity, duration, combined with strength training

Exercise & Reducing Risk of Alzheimer’s

- Normal adults with memory complaints (50 yrs+) (68.6 ± 8.7)
- 170 participants were randomized to 24 week exercise program (n=85) or usual care/education program (n=85)
- Change in ADAS cog over 18 months
- Found modest improvement (usual care deteriorated 1.04 pts; Intervention improved 0.26 pts; Overall difference was 1.3 points)

Baker et al. 2010. Effects of Aerobic Exercise in MCI. Arch Neurol
Physical Activity- What to do

And what we tell our older patients......

- Many of us are not athletes or not currently athletic
- Work up to a walk 15-20 minutes, 2-3 x week
- Mix it up! Walk, bike, swim, get outdoors, have fun
- Activity can take other forms: gardening, raking leaves, taking stairs whenever you can
Physical Activity - What to do

- NIH Website to help you get started
  [www.nia.nih.gov/Go4Life](http://www.nia.nih.gov/Go4Life)
- 4 types of exercise
  - Aerobic (walking)
  - Strength (weights)
  - Flexibility (yoga)
  - Balance (tai chi)
- Physically activity is important – whether formal exercise or not
- Bottom line: find something you enjoy doing and make it a regular part of your routine
Physical Activity - What to do

- Before starting a new exercise regime, consult your doctor.
- Three questions to ask:
  - Are there exercises I should avoid?
  - Is my preventative health up to date?
  - How do my health conditions affect my ability to exercise?
- Your doctor can help you select activities that are right for you and reduce risk.
Step 4: Watch what you eat!

**Rationale:**

- Healthy diet offers protection from cardiovascular disease
- Cardiovascular disease and obesity are associated with increased risk of strokes and Alzheimer’s disease
- Antioxidant intake from fruits and vegetables may protect against brain injury due to oxidative stress
Step 4: Watch what you eat!

- Our own work in Cache County\(^1\) Utah points to the importance of a healthy *dietary pattern* rather than vitamin supplementation
  - Diets such as the **DASH diet** or the **Mediterranean diet**, both of which emphasize eating vegetables, fruits, whole grains, and lean sources of protein and dairy reduces risk of cognitive decline and AD
  - Recent multinational clinical trials\(^2\) of 27,860 men and women indicate healthy eating (*cardiovascular scale akin to Med Diet*) and reduced risk of cognitive decline

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Diet & Nutrition: What to do

- NIH provides useful guides to diet and health
  http://nihseniorhealth.gov/
- If you have a health condition, check with your doctor or a dietician for what foods to avoid
- Begin by making one change at a time
  - Limit sugar intake
  - Take salt shaker off the table
  - Switch to whole grain
  - Add fish to the diet
Step 5: Work your brain- engage it in novel ways
Cognitive Engagement: Evidence

- **Epidemiological evidence** suggest that engaging in cognitively stimulating activities—NOVEL activities (i.e. new way of thinking/challenging) in mid- and late-life is associated with better cognitive outcomes.

- **Animal work** also shows increased synaptic plasticity when animals are housed in rich versus impoverished environments.

- **Clinical trial:** ACTIVE study “Advanced Cognitive Training for Independent and Vital Elderly” Randomized control trial of 170 healthy participants. Persistent improvement in speed of processing 10 years later (Rebok et al., 2014 J Am Geriatric Society)
Cognitive Engagement: Evidence

- Clinical Trial
  - Newcastle on Tyne, NE England (n=30)
  - Assigned participants to 8 weeks of exercise, puzzles, or art class; 3 hours week
    - Physical health improved with exercise;
    - Puzzle performance improved with puzzles;
  - Art class led to highest level of satisfaction and sustained activity
    - Social engagement and challenging, novel activity with sense of mastery & accomplishment
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Brain Fitness- Computer gaming???

Small short-term effects particularly if done as group activity.....

Jury is out whether effective & currently no solid evidence that delay disease or effects of aging


Asking right question...

- Some emerging evidence
  - Trying **new** things & **challenging** the brain is key
- Mayo Clinic Study of Aging\(^3\)
  - Artistic
  - Social activities
  - Computer use*

Begun in mid or *late life protect against MCI
- among persons 85-89 followed every 15 months for 3-6 years.

Step 6: Stress reduction & caring for your emotional health

- Growing evidence from animal models that stress hormones contribute to risk of cognitive decline and dementia

- Sleep also important for reducing toxic molecules including beta amyloid.

- Methods for reducing stress
  - Social engagement
  - Outdoor activity
  - Pet therapy
  - Meditation/prayer
  - Close personal connections
  - Getting help when none of these work

Step 7: Be apart of the solution...participate in research!

- Medical science has come a long way in the last 30 years
  - But still no cure for Alzheimer’s disease

- Preventing Alzheimer’s disease can only come with further research
  - Aimed at treatments that can be implemented early, safely, engaging the right targets and stabilize cognition and AD biomarkers

- Important to recognize that as we age, we are all at risk. And we will all be affected either directly or indirectly... We are all in the same boat
- Visit alz.org to register on line
- Hear about studies enrolling in your area
- Sign up for enews to receive regular news briefs about Alzheimer's care, research and events in each issue.
- And also receive up-to-date information on Alzheimer's research as it happens.
What to Expect if You Volunteer

- Benefits of Participating
  - Allows to take action against disease & be part of their solution
  - Access... to novel therapeutics and information
  - Looks ahead for the next generation
    - And gives hope for those fighting this disease
What to Expect if You Volunteer

- Not all trials test drugs
  - Some trials are to test new methods to advance early detection
  - Some test non-drug interventions: lifestyle, behavioral therapy or new methods for changing brain health (e.g. TMS)

Yoga feasibility studies
Duke Studies:
Retinal Imaging to Detect AD

- Study conducted by Duke Department of Ophthalmology and Bryan ADRC
  - Based on the idea that inflammation of retina (the light-sensitive layer at the back of the eye) is similar to brain inflammation in AD, and may identify individuals at risk of AD before memory impairment is evident
  - Retinal images may become an important tool in early diagnosis of AD

- Study involves a two-hour visit with complete retinal exam at the Duke Eye Center, at no charge to participant.
  - Current need for participants with mild cognitive impairment with memory loss

- If interested, please contact:
  - Cecilia Santiago-Turla (919-668-0634)
Duke-UNC-CH

Hybrid Brain Imaging Method- increasing diagnostic reliability (PET/MRI) in MCI

- Study to better understand adaptive change in Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD)
  - Advances in brain imaging using magnetic resonance (MR) imaging and positron emission tomography (PET) show promise in diagnosing early AD.

- In this study, we will combine methods (PET/MR) to enhance early MCI-AD detection.
Cache County - Gray Matters Study
(USU & Ulster University- Norton et al, 2015)

- Study Utah, Duke, and Ulster University (Ireland) examining practical approaches with emerging technologies that will lead to sustained behavior changes in six domains of brain health
  - Diet, exercise, cognitive stimulation, social engagement, stress reduction, sleep
  - Customized, evidence-based health information & activity monitor
  - Uses smartphone app

Is it Alzheimer’s? What can I do about it?

A lot you can do about it:
1) Mindset shift - you matter
2) Treat what you can treat
3) Get active
4) Watch your weight & diet
5) Keep mind active with new things
6) Stress reduction & sleep
7) Help in research
Where to turn when patients and families need assistance...

- Useful resources:
  - Alzheimer’s Association
    - [www.alz.org](http://www.alz.org) 800.272.3900
  - Area Agencies on Aging - Virginia
  - Family Support Program at Duke University:
    - DukeFamilySupport@duke.edu
    - 919-660-7510 or 800 672 4213
  - Bryan Alzheimer’s Disease Research Center
    - adrc@mc.duke.edu
    - 866-444-ADRC (2372)
Bryan ADRC
AD Prevention Registry

Be a part of the solution!
Every participant makes a difference!

ADRC (866-444-ADRC or visit our website: http://adrc.mc.duke.edu)
The Bryan ADRC
THANK YOU