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ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

ADNI Exclusive

A Special Newsletter for Participants in the Alzheimer's Disease Neuroimaging Initiative

Spring 2013

Dear Friends and Fellow Trialists:

Michael Weiner, M.D.
Fellow Participant & ADNI Principal Investigator

I have been involved in Alzheimer's disease (AD) research for 25 years – a relatively short time in some disease-specific medical research, but a considerable amount of time in relation to AD clinical research. Since I began to work in the field there has been remarkable improvement in the public's understanding and perception of AD. I also hope we are approaching a tipping point in public investment in AD research, treatment and care.

The nation's quickly changing age demographics have helped to focus attention on AD. As the ADNI community knows, age remains the biggest risk factor in the development of the disease. We are living longer, just as our population is getting older, and one in five people in the US will be over the age of 65 by 2050.

The statistics from our friends at the Alzheimer's Association are very convincing:

- AD is the sixth leading cause of death in the U.S.
- AD is the only disease among the top 10 leading causes of death that cannot be treated or even slowed.

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For more information email us at
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FDA offers New Guidance on Developing Alzheimer's Disease Drugs

By Michael Rafii, MD, PhD
Director, Memory Disorders Clinic
Associate Medical Core Director
Alzheimer's Disease Cooperative Study
University of California, San Diego

Medications can be categorized in one of two ways: symptomatic or disease-modifying. Symptomatic treatments reduce symptoms associated with a disease, but do not affect its course. For example, over the counter cold medications reduce the symptoms associated with a common cold, such as sneezing, coughing, runny nose, but they do not affect the duration of the cold. Patients can take those medications to feel a bit better, but they will still have the cold.

Disease-modifying drugs actually shorten the duration, or even stop the illness. Antibiotics are a great example. Taking an antibiotic will stop an infection, such as pneumonia. If an antibiotic is not taken, the pneumonia can progressively get worse, and even become fatal. There are other disease modifying drugs, especially in the fields on oncology and infectious disease, but also in neurology.

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Michael W. Weiner, MD (continued from page 1)

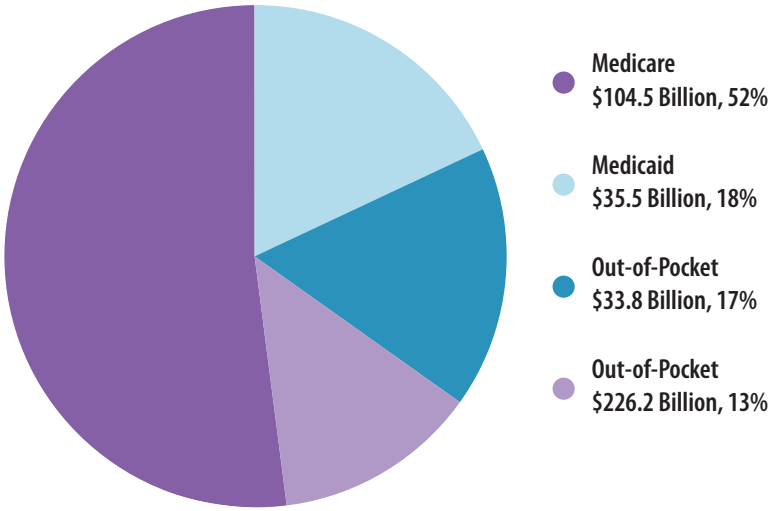
- More than 5,400,000 people in the U.S. live with AD.
- 10,000 baby boomers turn 65 every day in the U.S.
- 20% of the US population will be over 65 by 2050

With few exceptions, most public officials in the U.S., and people generally, agree with exponentially increasing the pace and scope of AD research endeavors while at the same time focusing on improving quality of life issues affecting current patients and caregivers. But we have to ask ourselves; does the general public understand the cost-benefit of investment in clinical research and caregiving issues? Again, I turn to our partners at the Alzheimer's Association:

- Today, for every $100 of federal investment in AD research - $28,000 will be spent on AD care
- If we can find a way to delay the onset or stop AD from progressing, we would be able to reduce health costs by $447 billion in 2050.
- If a treatment became available by 2015 to effectively delay the onset of AD for five years – the annual cost savings would be felt immediately in Medicare/ Medicaid annual savings of $42 billion by 2020.
- If a treatment became available to arrest AD in the mild to moderate stages – savings to Medicare/ Medicaid amount to $34 billion annually

Aggregate Costs of Care by Payer for Americans Age 65 and Older with Alzheimer's Disease and Other Dementias, 2012*

Total Cost: $200 Billion (B)



***Data are in 2012 dollars.**
Source: Alzheimer's Association 2012 Alzheimer's Disease Facts and Figures

While public awareness of AD issues has improved dramatically – we in ADNI are anxious to arrive at the tipping point and move quickly to the public health benefits (and extraordinary cost savings) offered by the development of AD treatments and prevention. There are excellent examples of public health issues garnering the interest of the American public to the point of active engagement and dialog. The results were new and robust public investment in research, treatment and care of the conditions at issue.

If you are my age, you may remember a time when the word "cancer" was never used in public. You may also recall several years during the 1980s when HIV and AIDS was known collectively as the "gay related plague". Look at where we are today in both diseases. Looking back, the affected communities took very different approaches to their public affairs campaigns.

Stories of the evolution in detection, treatment and care in breast cancer and in AIDS exemplify effective

advocacy and activism resulting in dramatic changes to related public policy and significant increases in the public's investment in research. In AIDS-related policy, the combination of stakeholder activism, media attention, advocacy and significant public education, was powerful enough to change the course of history in research and treatment of the disease. In the 1970s, a similar formula was applied by advocates in support of breast cancer research, treatment and education. As a result of the breast cancer initiatives, countless lives have been saved, treatments have become less aggressive and more effective, and the quality of life has improved dramatically for breast cancer survivors.

If you think research is expensive, try disease!

~ Mary Lasker

Both of these examples came as a result of broad-based public support for research and treatment in each of the diseases. Does any of this sound familiar?

It seems to me that AD care, research, and prevention are moving in the same direction. For instance, prior to this century, AD was not often discussed. People tended to use euphemisms like "old timers disease" or "senility" to describe AD. In addition, AD research and treatment issues have begun to garner significant media interest and growing attention from the public. This sea change in public attitude, attention and interest indicates that we are moving toward significant changes in AD-related public health matters.

As a stakeholder in AD research and treatment, I can see the confluence of AD public health issues, changing aging demographics, and public investment ahead. I think we will soon get to the AD policy tipping point. I truly believe that successful therapies are not that far off.

In closing, colleagues frequently remind me that ADNI is a gift that keeps on giving. I am passing this information on to you. As you know, in ADNI we are always looking ahead and anticipating developments to meet the demands of future clinical trial projects and related research. Because of your ongoing involvement, ADNI data and analysis continues to enhance efforts in the development of AD interventions.

In this newsletter we have contributions from Michael Rafii, MD, PhD, who serves as the Medical Director of the University of California, San Diego's Memory Disorders Clinic and is the Assistant Medical Core Director of the Alzheimer's Disease Cooperative Study. Mike writes about FDA guidelines on AD-related therapies and developments and discusses AD research in general in a Q & A session. In addition, we hear from Neelum Aggarwahl, MD, an ADNI investigator from Rush University in Chicago. Neelum takes a closer look at interesting gender-related findings from ADNI.

If you have any questions or comments regarding the content of this newsletter, please direct an email to us at brainlink@ucsd.edu. I look forward to writing to you again later in the year.

Michael W. Weiner, MD
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ADNI Principal Investigator & ADNI Participant
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(continued from page 1)

Current drugs that are FDA approved for dementia due to Alzheimer's disease (AD) fall into the symptomatic category. They certainly reduce symptoms associated with the disease, but they do not affect the course of the disease. And eventually, in some patients, the dementia becomes so severe, that the medications have less effect.

In February 2013, the FDA issued proposed guidance designed to assist companies developing new disease-modifying treatments for patients in the early stages of Alzheimer's disease, before the onset of the dementia stage of AD. At present, for drugs designed to treat patients with dementia, the FDA requires that treatments not only show an effect on abnormal thinking, but also how well patients function. The goal for existing clinical trials is to ensure that any beneficial effect on thinking is associated with a clinically meaningful outcome for the patient. The new proposal suggests that a biomarker may be used to assess the drug as well.

Because patients in the earliest stages of Alzheimer's disease, so called prodromal AD, have little, to no impairment of functioning, it is difficult to assess changes in function in these patients. This can make it difficult to determine if a given treatment's effect is clinically important. The FDA is aware of this, and is proposing a possible change to measuring outcomes in drugs being evaluated in patients with prodromal AD. A biomarker will be needed to show whether the drug is doing what it is supposed to be doing. For example, LDL cholesterol is a biomarker that can be measured and followed over time, to assess whether a statin drug is working. The critical point is that lowering LDL cholesterol is known to lower risk of heart disease.

There is a great need for such a biomarker in AD. However, as the FDA states, "no reliable evidence exists at the present time that any observed treatment effect on such a biomarker is reasonably likely to predict ultimate clinical benefit." This means that more work is needed to define such a biomarker for AD. But, the FDA is willing to consider using changes in a biomarker in conjunction with cognitive improvement by the drug. In essence, a positive biomarker result in combination with a positive finding on measure of cognition may support a drug's claim of disease modification in AD.

The question will be which biomarker should be used. And this question will need to be answered soon in order for such clinical trials to move forward. But the FDA proposal is very encouraging and reflects the knowledge we now have that we need to treat patients with AD in the earliest stages, before dementia sets in.

> "The goal for existing clinical trials is to ensure that any beneficial effect on thinking is associated with a clinically meaningful outcome for the patient."
>
> **Michael Rafii, MD, PhD**
> University of California, San Diego
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ADNI Analysis: Gender Differences in Grey Matter Atrophy

By Neelum T. Aggarwal, MD
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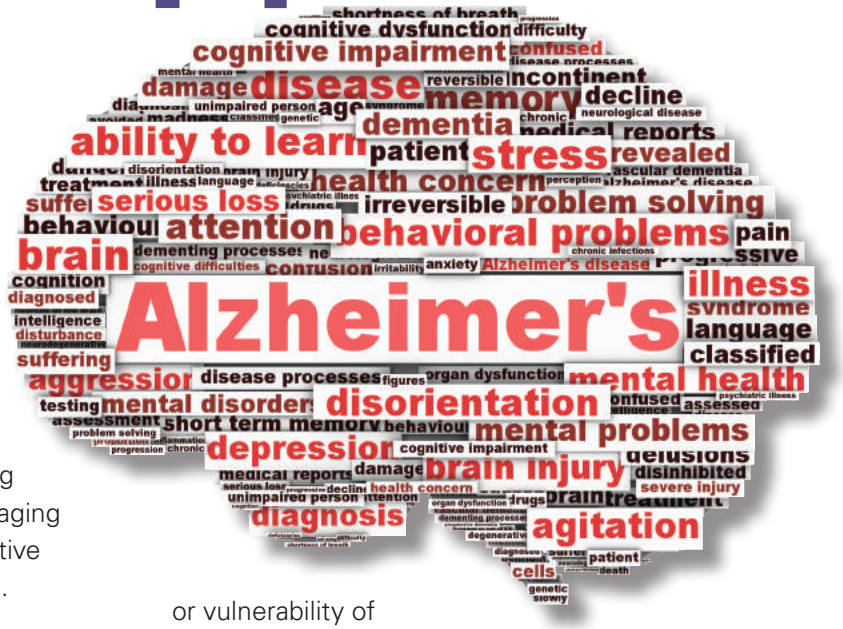

Recent data suggests that dementia, specifically AD, may be more prevalent in women than in men, and the basis for this may be in specific biochemical or neuro-anatomical changes in the brain. As I reviewed articles on this topic, I re-read an interesting paper by Skup et al. that examined multiple neuroimaging changes associated with specific diagnoses of cognitive function in men and women who participate in ADNI.

In the paper, a total of 687 persons (224 healthy controls, 266 amnestic MCI, and 197 probable AD) were evaluated for structural brain changes over a 2-3 year period, while remaining "stable" with regards to disease classification. The findings from this study were interesting in that gender differences regarding global and local volume measurements were noted in each of the diagnostic states (healthy control versus amnestic MCI versus probable AD). Females with AD and amnestic MCI differed from controls in the regions of the basal ganglia, specifically the right caudate nucleus – a finding not seen in males. Further, amnestic MCI females and males differed from AD males and females with regards to atrophy in the basal ganglia- thalamus - amygdale and precuneus. Lastly, gender differences were noted in the AD participants, in multiple areas such as the caudate, thalamus and bilateral middle temporal gyrus.

What do these findings potentially mean?

- First, they strongly suggest that not only are differences noted in brain anatomy between the two sexes for varying disease states (aMCI and AD), but that these differences can be seen in the deep structures of the brain – the basal ganglia – in addition to the cortex. Thus the relation of the basal ganglia to cognitive function may be a stronger predictor of risk or vulnerability of developing dementia and AD than previously thought.
- Second, gender brain changes and how they relate to cognitive function, may have larger implications, as they have the potential to inform clinicians and researchers how symptoms and long term consequences of disease differ among men and women.

Want to read more? Here are four articles that you may read to learn about this particular study or other research in this area.

Skup M, Ahu H, Wang Y et al. Sex Differences in Grey Matter Atrophy Patterns among AD and aMCI Patients: Results from ADNI. Neuroimage: 2011 June 1: 56

Sowell E, Peterson B, Kan E., et al. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cerebral Cortex. 2007; 17: 1550-1560.

Sullivan E, Rosenblom M, Serventi K. et al. Effects of age and sex on volumes of the thalamus, pons, and cortex. Neurobiology of aging. 2004: 25 (2): 185-192.

Witte A, Savli M, Holik A. Et al. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. NeuroImage 2010; 49 (2): 1205-1212.

Q & A with Michael Rafii, MD, PhD

Q: What AD research news do you expect in 2013?

A: There is a lot happening right now and 2013 promises to be as big as 2012 proved to be (see 2012 text below).

- Several new trials are preparing to launch – for instance both the intranasal insulin study (for MCI and mild AD) and the solanezumab trial (for people without cognitive impairment) are expected to start up this year.
- The AD community is eagerly awaiting the results from a Phase 3 clinical trial of IGIV in mild to moderate AD. Data is expected to be reported sometime later this year and additional trials are already underway.
- In addition, the launch of the Down Syndrome Biomarker Initiative (DSBI) will undoubtedly help us better understand how AD develops in Down Syndrome, and perhaps identify novel biomarkers of AD.

Q: Do you expect anything of note out of ADNI this year? Is ADNI reporting anything big?

A: We in the clinical research community love ADNI – and ADNI data and related analysis will be significantly enhanced later this year when the whole genome sequences for 800 ADNI participants becomes available to researchers worldwide.

The addition of the ADNI Whole Genome Sequence (WGS) will mark ADNI's crossover into a "big data" project, as mentioned in the Fall 2012 newsletter.

Moreover, new findings from ADNI are expected this year specifically related to identifying the earliest changes seen in the AD brain.

Q: It seems like we heard a lot about genes and AD last year, is that correct?

A: 2012 ushered in the identification of numerous AD susceptibility genes, as multiple genome-wide studies began delivering on the promise that sequencing large numbers of individuals will help identify mutations that increase the risk for AD.

The AD Genetics Consortium, reported genetic analysis of more than 11,000 people with AD and a nearly equal number of elderly people who have no symptoms of dementia. Three other consortia contributed confirming data from additional people, bringing the total number of people analyzed to over 54,000.

Until recently, only four genes associated with late-onset Alzheimer's had been confirmed, with the gene for apolipoprotein E-e4, also called APOE4, having the largest effect on risk. Findings in 2012 added another five – MS4A, CD2AP, CD33, ABCA7, and EPHA1, thereby doubling the number of genes known to contribute AD.

Later in the year, an additional susceptibility gene was identified, TREM2, also using genome-wide sequencing. The manner in which these genes contribute to AD are being carefully scrutinized, as each may represent a potential therapeutic target.

Q: Wow, It sounds like the gene news was pretty big last year…

A: And I haven't even talked about the biggest gene news in 2012 yet!

Q: OK, we saved the best for last. What was the biggest AD gene news last year?

A: Perhaps the biggest discovery in 2012 was the identification of a mutation in APP that significantly decreases its cleavage by beta-secretase, leading to 40% less production of beta-amyloid. This mutation also confers resistance to the development of AD in patients. That is, people with the mutation make substantially less beta-amyloid and do not get AD.

Just to review, all neurons secrete a protein called Amyloid Precursor Protein (APP), and APP is cleaved by two scissor-like proteins, gamma

secretase and beta secretase. This leads to the production of beta-amyloid, a toxic protein fragment that accumulates in the brain over time, causing brain cell damage, eventually leading to dementia, and deposits into amyloid plaques. Genetic mutations in either APP or either one of the scissor-like secretases that cleave it lead to inherited forms of Early Onset AD that strike patients in their 30s and 40s.

You may recall the gene for APP resides on the 21st chromosome, and in people with Down Syndrome, who are born with an extra copy of the 21st chromosome, each of their brain cells produce 50% more APP and subsequently 50% more beta-amyloid and therefore have a much greater incidence of AD. Intriguingly, individuals with Down Syndrome who have an extra-copy of the 21st chromosome, but lacking the segment that includes the APP gene, do not seem to get AD.

Q: That is big news. Is there more news from trials and studies?

A: We saw the launch of an unprecedented clinical trial in 2012, being run by an international collaboration of researchers in academia and industry to prevent dementia due to AD by treating patients with a drug before any cognitive symptoms appear. The trial, called the Alzheimer's Prevention Initiative (API) is being led by Eric Reiman, MD at the Banner Alzheimer's Institute in Phoenix, Arizona, and Francisco Lopera, MD and colleagues at the University of Antioquia in Colombia.

Over the past two years these scientists and other colleagues have enrolled members of the world's largest kindred afflicted with a mutation that leads to early onset AD.

On another topic I should talk about the flurry of results from multiple Phase 3 trials for AD. The results of two Phase 3 trials of intravenous bapineuzumab, a monoclonal antibody against beta-amyloid, showed that it failed to meet its primary endpoints in patients with mild to moderate AD.

However, data from Eli Lilly's solanezumab study, as well as the independent ADCS analysis of the trial, showed that the drug slowed down the rate of cognitive decline in patients with mild AD by about 34%.

Moreover, in looking at subjects who had positive amyloid PET scans, there was a statistically significant change in total beta-amyloid in cerebral spinal fluid (CSF). Both of these findings are quite exciting, and indicate that this anti-beta amyloid drug has a statistically significant effect on cognition, and a biomarker of AD; a first in AD research. The protocol for the Phase 3 study of solanezumab is being drafted now.

The trial will be commonly known as the A4 trial (Anti-Amyloid Therapy in Aysymptomatic AD) .

Last year, we saw the end of the gamma-secretase inhibitor, avagacestat, which followed in the footsteps of another drug in the same class, semagacestat. Both were shown to have trends towards worsening cognition as an adverse effect. Meanwhile beta-secretase inhibitors, as well as gamma-secretase "modulators" move forward in the drug pipeline, and are thought to hold great promise.

Finally, the FDA approval of Amyvid as an amyloid imaging tracer for PET scans represents a major milestone in the clinical evaluation of AD. Other tracers are being developed and may be approved this upcoming year.

BRAIN TEASERS

Commonyms – What do these words have in common?

1. A Ball – A Fish – A Cold
2. A Ball – A Salad – A Coin
3. A Cork – A Question – A Balloon
4. A Bottle – A Baseball Player – A Mushroom
5. A Bell – Mouth – A Shoe
6. A Tug of War – The Nightly News – A Boat

Commonym answers: 1. They are caught; 2. They are tossed; 3. They are popped; 4. They have caps; 5. They have tongues; 6. They have anchors.

Mad Gabs (Hint: sound out the sentence)

1. Abe Odd Hull Up Hop
2. Abe Rye Tidy Yeah
3. Abe Who Beat Wrap
4. Able Ankle Hook
5. Able Hiss Heard

Mad Gab Answers

1. A Bottle of Pop
2. A Bright Idea
3. A Booby Trap
4. A Blank Look
5. A Blizzard