

Alzheimer's Disease Information Network ADIN Monthly E-News

Alzheimer's Disease
Cooperative Study
August 2012
No. 45

CTAD 2012

5th Conference

Clinical Trials in
Alzheimer's Disease

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Grimaldi Forum

The early registration
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CTAD 2012

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This newsletter is prepared monthly by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. Content is intended to educate the public about AD research endeavors and other AD issues.

Questions or com-
ments?
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Observations from the Alzheimer's Association International Conference (AAIC)

By Michael Raffii, MD, PhD
Director, Memory Disorders Clinic
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Though the national news media covered the major research announcements coming out of AAIC last month, there are a couple of results that deserve a closer look.

One group of medications that are being evaluated for AD is called nicotinic agonists. The drugs amplify the effects of acetylcholine, a main neurotransmitter that is essential for normal memory function. Acetylcholine is severely reduced in people with Alzheimer's and the currently FDA-approved drugs for AD work by increasing Acetylcholine levels in the brain.

EVP-6124 (EnVivo Pharmaceuticals) is a selective, partial, alpha-7 nicotinic agonist that, in previous testing, has demonstrated cognitive benefits in normal volunteers and in preliminary study participants with AD.

The company conducted a 6-month, double blind, placebo-controlled, Phase 2b study of three doses of EVP-6124 in 409 people with mild to moderate Alzheimer's who were either on stable Alzheimer's therapy (donepezil or rivastigmine) or on no therapy.

Primary efficacy endpoints were two established and accepted scales for measuring memory, language, attention and other cognitive abilities. Additional pre-specified endpoints included several measures of cognition, language, mood, and ability to function independently.

After 23 weeks of treatment, the researchers found that, compared to the placebo group, the 2 mg treatment group had statistically significant benefits on tests of cognition. They also saw a significant effect on scales of functioning. They reported that EVP-6124 was safe and well tolerated with some mild to moderate gastrointestinal side effects in a minority of patients in both the 1 and 2 mg dose groups. The drug will most likely move into a Phase 3 study, which is the last step towards possible FDA approval.

Another exciting development in clinical trials for AD was from the extension study of the Phase 2 trial of IGIV. As you may recall, it has been known for some time that IVIG, which is derived from human blood, contains antibodies that bind to the beta amyloid protein. Each dose of IVIG contains pooled antibodies extracted from the plasma of more than 1,000 blood donors.

Results from previous work show that IVIG appears to promote the clearance of beta amyloid from the brain and block its toxic effects on brain cells resulting in a stabilization or improvement in cognition and functioning of patients with Alzheimer's disease.

Results from the extension study of 16 of the original 24 subjects who were in the phase 2 trial of IVIG were presented. The 24 participants in that study received six months

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AAIC Roundup continued ...

of treatment followed by a 12-month open-label extension where all subjects received IVIG. Sixteen of the originally enrolled subjects received treatment for 36 months, including five originally given placebo and 11 treated with various doses of IVIG.

Study participants who were treated with IVIG every two weeks for the full 36 months had the best outcome, with no decline on several standard measures of cognition, memory, daily functioning and mood at the three year endpoint. As a group, the 11 participants who received IVIG for the full 36 months had favorable outcomes in terms of their thinking abilities, behavior and daily function. The five participants who were initially treated with a placebo and then switched to IVIG declined while on placebo but experienced less rapid decline while receiving a uniform dose of IVIG. The results of the Phase 3 trial should be reported some time next year, and it is hoped, will confirm these findings in a much larger number of subjects.

ApoE4's Different Effects in Men and Women

By Michael Rafii, MD, PhD
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For every three women with Alzheimer's disease, only about two men have the neurodegenerative disorder. And although women live longer than men do, on average, the disparity persists even if you correct for the difference in longevity. In a paper published June 13 in the *Journal of Neuroscience**, research suggests that ApoE4 status may be the source of this difference, as it has different effects in healthy women versus men.

The main finding is that apoE4 disrupts brain function in healthy, older women but has little impact on brain function in healthy, older men. Women carrying a copy of apoE4 show brain changes characteristic of AD that can be observed before any outward symptoms manifest.

To come to this conclusion the researchers obtained functional MRI scans of 131 healthy people, with a median age of 70, to examine connections in the brain's memory network. They found that in older women carrying the apoE4 allele, this network, which normally shares a synchronized pattern of activity with other brain areas, exhibits a loss of that synchrony, and this is typically seen in Alzheimer's patients. But in men, the synchrony was preserved even if ApoE4 was present.

When the researchers checked spinal fluid (CSF), they found that the CSF of women, but not men, who carried at least one E4 allele was substantially enriched in tau, which readers of this blog will recall is an important marker of neurodegeneration in AD.

This study is quite important in that it opens up a new understanding of the interplay between ApoE and gender, and the observed differences in the incidence of AD between men and women.

*Greicius et al, Gender Modulates the APOE e4 Effect in Healthy Older Adults: Convergent Evidence from Functional Brain Connectivity and Spinal Fluid Tau Levels *The Journal of Neuroscience*, 13 June 2012, 32(24):8254-8262.

Early Results of IV Bapineuzumab Study

By Michael Rafii, MD, PhD
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The results of the first of four Phase 3 trials of intravenous bapineuzumab, a monoclonal antibody against beta-amyloid, show that it failed to meet its co-primary endpoints in some 1,100 patients with mild to moderate Alzheimer's disease who carry at least one ApoE4 gene.

Three other trials are still underway. Pfizer is conducting a second Phase 3 trial in ApoE4 carriers in Europe. Janssen AI is leading two Phase 3 studies of patients who are ApoE4 carriers and non-carriers at sites primarily in North America. Pfizer is conducting two Phase 3 studies of patients who are ApoE4 carriers and non-carriers at sites primarily outside of North America, the first of which was presented yesterday.

The breakdown in ApoE4-carriers versus non-carriers is important because there is a feeling that the drug might work better, if at all, in patients who do not carry the ApoE4 gene. Readers of this blog will recall that ApoE4 status is associated with an increased risk of cognitive decline and elevated amyloid deposition. It is believed that the different forms of ApoE (2, 3 and 4) appear to regulate the removal of beta-amyloid from the brain, and they do so with different efficiencies. It has been shown that ApoE4 seems to be the slowest in removing beta-amyloid from the brain, which may be why it confers the most genetic risk.

Why did the trial fail? A useful analogy might be to think of heart disease.

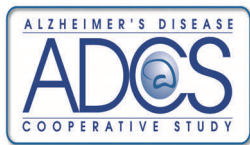
High cholesterol levels are associated with a higher incidence of heart attacks. However, a patient does not present to their doctor with any symptom associated with high cholesterol. In fact, until 25 years ago when cholesterol levels started to be routinely checked, many patients would present with a heart attack as the first symptom of their long standing high cholesterol levels. The same is thought to be true about AD.

The symptoms of dementia are to the brain much like a heart attack is to the heart. By the time the symptoms of dementia have developed, there have been years of an underlying pathological process affecting the brain, namely the accumulation of beta-amyloid and the loss of synapses and neurons. And, much the same way, if a patient presents to an emergency room with a heart attack, prescribing a cholesterol lowering medication for the first time may be too late. Specifically, 15-20 years too late. Now that we can check cholesterol levels earlier in life with a simple blood test, in the absence of any symptoms, we can start patients on cholesterol lowering medications to reduce their risk of having a heart attack in the first place.

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The same is believed to be true about treatment of Alzheimer's disease dementia. By treating Alzheimer's disease early, by lowering beta-amyloid levels, we may be able to prevent the dementia phase from ever developing. ApoE4 carriers have more amyloid in the brain and are further along the pathological cascade that leads to dementia, and may not respond as much to amyloid-lowering drugs as non-ApoE4 carriers.

We eagerly await the results from the remaining phase 3 studies of Bapi, in particular the effects on non-ApoE4 carriers.



New Research Indicating Gait Changes Could Signal Increased Risk for Cognitive Impairment

Gait disturbances – such as a slowing of walking pace or a more variable stride – could indicate a decline in cognitive function, according to new research studies reported at the Alzheimer's Association's International Conference® 2012 (AAIC® 2012).

Difficulties with walking are not inevitable consequences of aging. They are, however, common and relevant problems among older adults. Research shows that people with walking difficulties not only have an increased risk of falling, but may also have an increased risk developing memory disorders and dementia.

Stephanie A. Bridenbaugh, MD, of the Basel Mobility Center in Basel, Switzerland, and colleagues used quantitative gait analysis to explore this issue. The study followed 1,153 participants (average age=77) including outpatients from the Basel Memory Clinic and Basel Mobility Center, plus cognitively healthy participants in a Basel cohort study, from 2007 to 2011.

Participants were divided into groups based on their cognitive diagnoses: cognitively healthy, mild cognitive impairment (MCI) or Alzheimer's dementia. Those with Alzheimer's dementia were subdivided into mild, moderate or severe. Gait was measured using a 10-meter-long electronic walkway with almost 30,000 integrated pressure sensors. All participants performed one "normal" walk and two different "dual tasks" – normal walking while simultaneously counting backwards out loud or while simultaneously naming animals.

The scientists found that gait became slower and more variable as cognitive decline progressed. For all groups, walking speeds were slower during dual tasking than during normal walking alone. "Those with Alzheimer's dementia walked slower than those with MCI, who in turn walked slower than those who were cognitively healthy," said Bridenbaugh.

Specific Aspects of Gait may be Associated with Specific Cognitive Abilities and Functions

With aging and in people with Alzheimer's disease, various brain functions deteriorate. Most research has focused on cognition. Recent evidence suggests that gait is also affected by aging and Alzheimer's, yet the exact relationship remains unclear.

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Mohammad Ikram, MD, PhD, and colleagues at Erasmus MC, Rotterdam, the Netherlands investigated the relationship between cognition and gait in community-dwelling elderly. The researchers studied 1,232 individuals age 49 and older from The Rotterdam Study (Note: data included here is updated since the original abstract submission to AAIC 2012). Standardized neuropsychological tests were used to measure information processing speed, memory, fine motor speed, and executive function. Gait was assessed using an electronic walkway.

Each participant performed a normal walk, a tandem walk (where the heel of your front foot is placed directly touching the toes of your back foot), and a turn. Gait variables were grouped into seven independent factors:

- Rhythm (reflecting stride time and cadence)
- Pace (reflecting stride length and velocity)
- Phases (reflecting the amount of time spent on one or both feet)
- Variability (reflecting the variation in gait within persons)
- Base of Support (reflecting step width and stride width)
- Tandem (the amount of errors in a tandem walk)
- Turn (the amount of time and steps needed to turn around)

Interesting patterns emerged in the data analysis; the researchers found that certain cognitive domains were only associated with certain aspects of gait.

- Information processing speed was associated with the Rhythm aspect of gait.
- Executive function was associated with Pace and Variability.
- Fine motor speed was associated with Tandem.
- Memory was not associated with any aspect of gait.

"Our results suggest that cognition and gait are tightly linked according to a specified pattern, in which certain cognitive domains only associate with corresponding aspects of gait," Ikram said.

Reduced Gait Velocity, Cadence, and Stride Length may be Associated with Cognitive Decline

Some previous studies have reported that gait abnormalities may be associated with cognitive impairment and dementing illnesses. However, it is unclear which gait components may be associated with a future cognitive decline.

Rodolfo Savica, MD, MSc, and colleagues at the Mayo Clinic Study of Aging (MCSA) measured the stride length, cadence and velocity of more than 1,341 study participants through a computerized gait instrument (GAITRite) at two or more visits roughly 15 months apart. The visits also included neurological and neuropsychological evaluations covering four domains: memory, executive functioning, language, and visuospatial ability. Participants were either cognitively normal (1,172), or diagnosed with MCI (158) or dementia (11).

The researchers found that study participants with lower cadence, velocity and amplitude of the stride length experienced significantly larger declines in global cognition, memory and executive function.

"We observed an association between reduced gait velocity, cadence and stride length, and both global and domain-specific cognitive decline in our population," said Savica. "These results support a possible role of gait changes as an early predictor of cognitive impairment."

Continuous In-Home Monitoring may be a More Accurate Measure of Gait than Single Tests

Traditionally, walking speed has been collected at a single, intermittent time point, such as during a yearly physical exam. "Advanced technology now allows us to measure walking speed in one's own home, derived from hundreds of walking episodes, and using information collected continuously by motion sensors," said Lisa Silbert, MD, MCR, of Oregon Health & Science University, Portland. "This potentially provides a better measure that links real-world walking abilities and brain health."

Silbert and colleagues worked with 19 dementia-free volunteers (mean MMSE 28.7) enrolled in the Intelligent Systems for Assessment of Aging Changes (ISAAC) study. All participants underwent brain MRI to measure the volume of the total brain and various brain sections. Gait speed was determined in two ways: (1) at the time of MRI, by assessing the time to walk nine meters, and (2) by using an in-home assessment system that continuously collected data over a one month period using motion activity sensors.

The researchers found that:

- Study participants walked faster when measured once in person than when walking in their home under conditions of continuous assessment.
- Slower walking speed determined with continuous in-home assessment technology was associated with smaller total brain size, while single walking speed measures were not.
- Slower in-home walking speed was more highly associated with smaller volumes of the hippocampus (a section of the brain important for memory) than walking speed obtained during a single time point.

"Walking speed taken at a single time point may over-estimate walking abilities in the elderly. Our data suggests that continuous in-home monitoring may provide a more accurate reflection of walking speed and may be more sensitive at detecting motor changes associated with future cognitive decline," Silbert said.

Gait Changes Correlate with Dementia Symptoms in an "Old-Old" Population

The Kurihara Project, conducted by Kenichi Meguro and colleagues at the Tohoku University Graduate School of Medicine, Sendai, Japan, examined the relationship between gait and cognition in 525 community dwelling persons age 75 and older in Kurihara and Osaki, Japan.

Researchers gathered participants' demographics, medical history, general medical and neurological examination results, MRI results, and neuropsychological exams including the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR). Participants walked six meters at their fastest pace. Gate measures included gait pattern, velocity and stride length.

The researchers found that 385 study participants had a normal gait pattern, 65 had "neurological gait," and 73 had abnormal gait due to bone and joint disease (such as osteoarthritis). On the CDR scale: 175 participants were classified CDR 0, 287 as CDR 0.5, 44 as CDR 1, 20 as CDR 2, and 2 as CDR 3. (CDR 0 is considered normal, CDR .5 = very mild dementia, with dementia severity increasing to CDR 3 = severe dementia.) They also found that MRI-measured atrophy of the entorhinal cortex – a section of the brain that functions as a hub in a widespread network for memory and navigation – was significantly correlated with gait velocity.

"Our research found that gait velocity was significantly decreased as the severity of dementia symptoms increased," said Meguro. "Gait should no longer be considered a simple, automatic, motor activity that is independent of cognition. They are linked."

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Revolutionary project will obtain entire genome sequences in fight against Alzheimer's

Mark Wheeler
Senior Media Relations Representative
UCLA Health Sciences

Since 2004, UCLA's Laboratory of Neuro Imaging (LONI) has been responsible for receiving, organizing, archiving and disseminating the stream of data generated by the Alzheimer's Disease Neuroimaging Initiative (ADNI), an ambitious, worldwide effort by scientists to define the progression of Alzheimer's disease.

That stream of data will now turn into a flood, as LONI partners with an ambitious public-private effort to dig deeper into the causes of this devastating disease by obtaining the whole-genome sequencing of the more than 800 people enrolled in ADNI – the largest cohort of individuals related to a single disease.

This work is expected to generate at least 165 terabytes of new genetic data, an amount roughly equivalent to the information contained in 165,000 entire copies of the Encyclopedia Britannica. "This effort, involving almost 60 sites around the country, is the best chance we have for understanding this brutal disease," said LONI director Arthur Toga, a UCLA professor of neurology and one of the collaborators on the management of the sequencing efforts. "We collect vast amounts of imaging, cognitive and biosample data from hundreds of subjects with Alzheimer's disease, those at risk, and controls. One of the more unique aspects of this study is that all data are shared with any scientist, without embargo. We have already engaged many scientists around the world with this open access."

The new genome project is a significant extension of ADNI, which now enrolls people with Alzheimer's disease, mild cognitive impairment and normal cognition who have agreed to be studied in great detail over time. The goal is to identify and understand markers of the disease with the hope of improving early diagnosis and accelerating the discovery of new treatments.

All of the ADNI data continues to flow into UCLA's LONI, including detailed, long-term assessments of neuropsychological measures, standardized structural and functional imaging, and precise biomarker measures from blood and spinal fluid. Now, added to this wealth of information will be the ADNI participants' entire genome sequences, which determine all 6 billion letters in an individual's DNA in one comprehensive analysis.

Once the sequences are completed — approximately 16 weeks after the sequencing project starts — the raw data will rapidly be made available to qualified scientists around the globe to mine for novel targets for risk-assessment, new therapies and much-needed insights into the causes of Alzheimer's.

All of the information from ADNI has always been made freely available, without delay, to scientists; to date, this has resulted in more than 500 scientific manuscripts.

ADNI is a public–private research project led by the National Institutes of Health with private sector support through the Foundation for NIH. Launched in 2004, ADNI's public–private funding consortium includes pharmaceutical companies, science-related businesses and nonprofit organizations, including the Alzheimer's Association and the Northern California Institute for Research and Education.

The ADNI whole-genome sequencing is being funded through a partnership between the Alzheimer's Association and the nonprofit Brin Wojcicki Foundation, a charitable organization created by Anne Wojcicki, founder of the online genetics firm 23andMe, and her husband, Sergey Brin, co-founder of Google.

"Sequencing the ADNI participants and making the genetic data immediately available to researchers around the world will significantly improve our understanding and approach to Alzheimer's disease," Anne Wojcicki said. "The ADNI team and the Alzheimer's Association are impressive in their ability to quickly make decisions that are truly in the best interest of people with Alzheimer's."

"Linking these deep-sequencing data with imaging and other data may help solve the puzzles in Alzheimer's that still vex us," Toga said. "Certainly, a more complete picture will emerge, hopefully leading to effective therapies."

The Laboratory of Neuro Imaging at UCLA, which seeks to improve understanding of the brain in health and disease, is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function. It is part of the UCLA Department of Neurology, which encompasses more than a dozen research, clinical and teaching programs. The department ranks in the top two among its peers nationwide in National Institutes of Health funding.

A Mother's Love, Still Strong at 104



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In this photo shot by the [Herald Tribune](#), Rosario Schielzeth, 104 years old (right), is once again caring for her daughter Maria Garcia, 87. (Elaine Litherland/Herald-Tribune)



By NILS KONGSHAUG

June 15, 2012

It's a deal that has worked throughout human history: Your parents take care of you when you are little and you return the favor when they are old.

But sometimes the usual arrangement is turned on its head.

Maria Garcia is 87 years old. After a rich and rewarding life, she is now suffering from dementia. The person she depends on more than anyone else in the world... is her mother.

Her mother, Rosario Schielzeth, turned 104 this week. Her daughter had to be reminded every few minutes who the birthday balloons were for. And Rosario didn't mind answering, every time.

"She has the patience of a saint," says Maria's son and Rosario's grandson, Albert Garcia.

Albert, 60, describes his mother's condition as "happy-clappy dementia," because she is never angry or upset. But like anyone with Alzheimer's Disease, she can be trying, asking the same questions over and over.

"My grandmother has to live with her 24-7," Albert says. "Not once have I seen her roll her eyes or answer curtly."

Since Rosario gave birth to Maria in 1925, the two women have almost never lived apart. When Maria was starting her own family, she had her own home, but it was across the street. And most of her life, she and her mother have lived under the same roof.

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These days, that roof is in Sarasota, Fla. Every morning, the two women sit down to a leisurely breakfast. Rosario reads the paper and tells her daughter what's going on in the world, to keep her mind sharp.

"I talk all the time to her," Rosario says. "That's the best thing for people in that situation. Talk all the time."

Rosario herself has no trouble with her memory, or with anything else. She needs a walker to get around, but she doesn't wear a hearing aid. She doesn't even need glasses after having cataract surgery a few years ago. Apart from vitamins, she takes only one pill a day, a mild blood-pressure medication.

When people ask what's kept her going all these years, she tells them she watches what she eats and stays away from doctors. .



Maria Garcia and her mother Rosario Schielzeth in 1942

Rosario has been taking care of other people her whole life. When she was a girl, living in Costa Rica, it was her siblings. She was one of ten children, so the older ones had to pitch in. Then it was her own children, and then her grandchildren.

When Albert was a baby his musician father, whom he describes affectionately as "a Puerto Rican Clark Gable with a pencil moustache," ran off with a stewardess. His grandmother, living across the street, "did the wash for both houses, cooked for both households," so his mother could go to work.

Not that her whole life was self-sacrifice. She had a passion for travel and even though her husband didn't, she managed to see much of the world.

He earned enough as a cabinet maker to support the family, so she went to work as a seamstress to earn travel money. With her girlfriends she took off for Thailand, Venice, Rome, Switzerland....

These days her journeys are more proscribed: the movies, the mall, the beach for ice cream.

But she can still enjoy her other great passion: Bingo. She and her daughter play at least six rounds every night.

Carol Festari, a live-in caretaker for both women, also joins the games. She says Rosario wins nine times out of ten.

They play for candy, to Rosario's regret. "Imagine if we were playing for money," she tells them. "You'd both be broke."

Festari says the first thing Maria says when she wakes up and the last thing she says before she goes to bed is, "Where's my mother?"

Her mother is always there.

<http://abcnews.go.com/US/mothers-love-strong-104/story?id=16571400>

Meeting Unveils NIH Neurological, Behavioral Toolbox for Clinical Research

Registration is now open for "Unveiling the NIH Toolbox", a free scientific conference Sept. 10-11 presenting the **NIH Toolbox for Assessment of Neurological and Behavioral Function**—a set of brief but comprehensive neurological and behavioral health measurements designed for use particularly in large-scale research studies such as epidemiological studies or clinical trials. Developed by a team of more than 250 scientists from nearly 100 academic institutions, the NIH Toolbox provides a battery of on-line and royalty-free measures of motor, cognitive, sensory and emotional function for study participants aged 3 to 85 years. Developed under the auspices of the NIH Blueprint for Neuroscience Research, a coalition that creates new tools and resources to advance neuroscience research, the highly anticipated NIH Toolbox promotes economies of scale and enhanced efficiency in measurement.

Taking place in Bethesda, Md., the meeting features lectures, interactive demonstrations and panel discussions about the development, testing and use of the NIH Toolbox in biomedical research. An optional "Administering the NIH Toolbox" training workshop follows the conference on Sept. 12-15. To register for the conference and/or training workshop or to learn more about the NIH Toolbox please visit:

www.nihtoolbox.org.

ADCS Trials Enrolling...

ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments.

<http://adcs.org/Studies/ImagineADNI.aspx>.



Resveratrol for Alzheimer's is Recruiting

Resveratrol

 for Alzheimer's Disease

<http://www.adcs.org/Studies/RES.aspx>



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