Gruppo di ricerca geriatrica

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28 NOVEMBRE 2013

MITI E REALTA' DEL TRATTAMENTO DELLA DEMENZA DI ALZHEIMER

Good news on dementia prevalence—we can make a difference

Sube Banerjee

www.thelancet.com Vol 382 October 26, 2013

Dementia is a powerful example of the complexity and long-term nature of the disorders that are now the major outstanding challenges for health-care systems. Those with dementia are generally an old and frail population with multimorbidity; data from the Scottish School of Primary Care suggest that only 17% of people with dementia have no other long-term disorder. If we can get services right for dementia, then we will be a long way towards getting them right for all individuals with complex and long-term disorders. The CFAS results suggest that prevention is possible and that we can have agency in this most complex of disorders. These findings should spur us on, to go further and faster in secondary and tertiary prevention as well as primary prevention in dementia, for the benefit of all. This study shows that we can all make a difference.

Corriere della Sera **Sabato 26 Ottobre 2013**

l'inchiesta 4 Alzheimer in Italia

STORIE DI MEMORI

Qual è l'età dei vostri neuroni?

Le cellule del cervello (in buona parte) hanno la vostra età. Nel resto del corpo c'è molto ricambio, confermato da uno studio del Karolinska Institute a Stoccolma. I globuli rossi durano 120 giorni (dopo aver percorso 1.500 km). In un adulto lo scheletro viene «rimpiazzato» nel giro di 10 anni

La frontiera (incerta) della cura: pillole, bambole e robot

Rino e Ricordina erano braccianti. Ennio e Silvana avevano una pizzeria. Antonio e Maria non si sa. Tre coppie, sei demenze. Come dribblare il dolore: ammalarsi insieme. Mirandola, Modena: terremoti e smottamenti della mente. I tre mariti al Nucleo Alzheimer del Cisa (Centro Integrato Servizi Anziani), le tre mogli avanti e indietro da casa (per ora). Stadi sfasati della malattia. Prima Antonio stava con Maria nell'appartamento del figlio e della nuora, tenuto sempre a letto (allettato) con sedativi e omogeneizzati (dei nipotini). Non sempre a casa si sta bene.

«Quando è arrivato da noi non riusciva più a camminare, bisognava imboccarlo — racconta Annalisa Bonora, psicologa responsabile del nucleo —. Abbiamo cominciato da capo». Meno pillole, più cure non farmacologiche. Antonio, 73 anni, napoletano, ha ripreso a mangiare da solo (di tutto). Cammina (anche troppo). Scarica l'aggressività nel giardino esterno. Dentro, nell'ambiente Snoezelen importato dall'Olanda, cercano di rilassarlo nella stanza multisensoriale con musica, profumi, colori, tubi a bolle. L'obiettivo è farlo vivere meglio, ritardare l'«allettamento» in una casa di riposo. Per un po' Maria è andata a trovare il marito con il figlio, fino a quando ha cominciato a perdersi intorno a casa. Adesso bisognerà pensare anche al suo Alzheimer. Antonio è migliorato, ma va comunque a periodi. Ennio invece «è irriconoscibile rispetto a un anno fa»: nella residenza sanitaria (Rsa) dove l'avevano piazzato con la sua demenza vascolare picchiava tutti, lo imbottivano di psicofarmaci. «È arrivato qui che non parlava — ricorda Giacomo Menabue, terapista della riabilitazione per i disturbi del comportamento — ripeteva meccanicamente "Ho la mamma nel cuore", vagava in continuazione. Abbiamo cominciato col mettere insieme i pezzi della sua storia». Ennio ha fatto molti lavori. Muratore, giardiniere. Dopo il terremoto del 2012 con le crepe che si sono aperte nei

deficit di servizi. Si parla tanto di cure non farmacologiche. La Snuezelen, la musicoterapia, la *doll therapy* con le bambole importate dalla Svezia, la foca robot giapponese Paro, che in una casa di riposo di Siena fa rinascere le parole sulle labbra di Roberto e il sorriso su quelle di Enrica... «Bisognerebbe che il sistema pubblico investisse per studiare la validità di queste pratiche» dice Nicola Vanacore, ricercatore dell'istituto Superiore di Sanità. Nel frattempo, ci si muove lungo la frontiera della sperimentazione. E le medicine? Al di là dei sedativi per i «disturbi del comportamento», l'armadietto dell'Alzheimer è lo stesso da 15 anni: quattro farmaci (tre inibitori della colinesterasi) che puntano a migliorare «la comunicazione» tra i neuroni, con effetti molto variabili (nel tempo e da persona a persona). In Francia il loro consumo è diminuito negli anni. Sono farmaci sintomatici, che non fermano il progresso della malattia.

Il miraggio della guarigione

Quando si potrà guarire dall'Alzheimer? Il *Corriere* ha parlato con Luca Santarelli, capo del settore Neuroscienze della Roche, e Iain Chessell che guida la ricerca per Astrazeneca. I loro team, come quelli di altri giganti farmaceutici (Lilly, Pfitzer etc) stanno studiando il

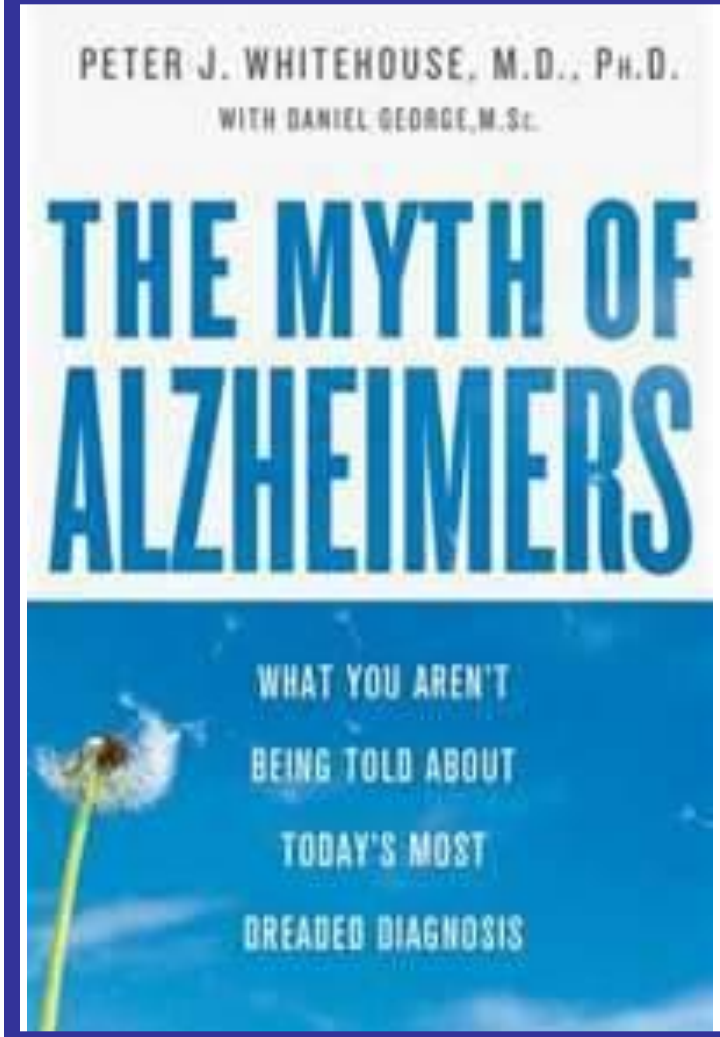
L'ansia di Rino e i bulloni

Rino si rilassa svitando bulloni, quando è agitato ripete «adesso devo morire».

Una storia complessa
da Auguste D. in poi …

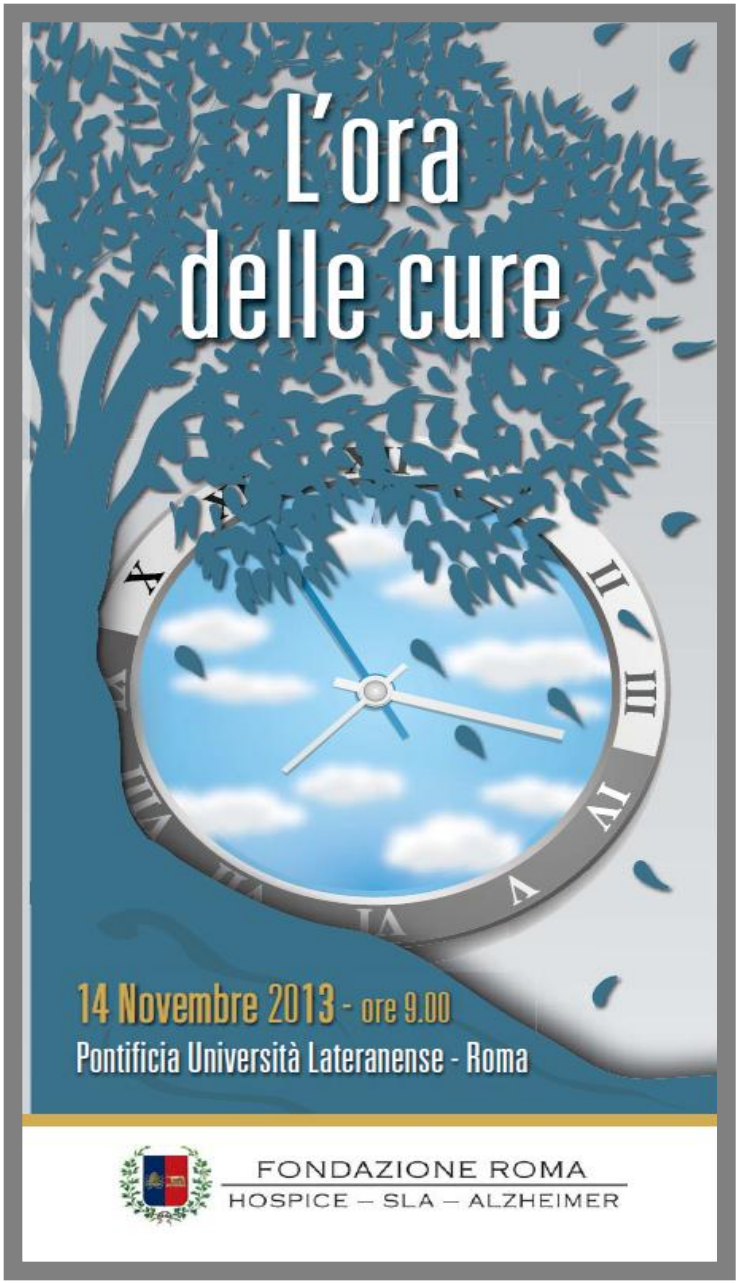
Fino alla metà degli anni ’70 la malattia di Alzheimer venne considerata una condizione rara; nel contempo il declino cognitivo degli anziani veniva attribuito genericamente a processi arteriosclerotici.

Attorno alla metà degli anni ’70, l’accumularsi delle conoscenze portò al riconoscimento del fatto che la malattia di Alzheimer e la demenza senile erano essenzialmente la stessa malattia.



January 2008

Lo stigma dell'inguaribilità attorno all'Alzheimer.
Ma quanto sono di fatto le malattie realmente guaribili?
L'esigenza di un "accompagnamento clinico" senza fine, per una storia naturale che tende ad allungarsi.


L'ora
delle cure
14 Novembre 2013 - ore 9.00
Pontificia Università Lateranense - Roma
FONDAZIONE ROMA
HOSPICE – SLA – ALZHEIMER

Una tipologia delle cure che riconosca le dinamiche complesse della sofferenza … non è un mito…

The field of geriatric medicine must embrace the opportunities that healthcare reform presents and the growing attention to futile care at the end of life. "Futile care" must be meticulously defined. Care that can extend the life of a person with dementia is not necessarily "futile". Innovative interventions to prevent futile care are sorely needed. By actively participating in interprofessional initiatives with colleagues in nursing, palliative care, rehabilitation medicine, emergency medicine, and related disciplines, geriatrics can make major contributions to improving the care and quality of life of NH residents with severe dementia.

Finucane TE et al, J Am Geriatr Soc 61:1804-5, 2013

… nemmeno è futile aiutare i caregiver

“Come aiutarla? Non si sa bene come. Mentre è assai pesante vivere con lei: non tanto i singoli momenti, a uno a uno, della vita insieme, com’è diventata, quanto la routine. A volte nel guardare alla prospettiva, anche prossima, delle giornate, mi prende la disperazione. Non c’è quasi un piccolo spazio di libertà, per me. E sono sempre stanchissimo. L’unico rimedio è l’amore: amare davvero, sino in fondo, attivamente, utilmente (quanto è possibile). Sì, ma a un certo punto è difficile. Troppo difficile: perciò lo si deve chiedere a Dio”.

S. Mannuzzu, 2013

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2010;30:161–178
DOI: 10.1159/000316119

Accepted: May 26, 2010
Published online: September 10, 2010

Nonpharmacological Therapies in Alzheimer's Disease: A Systematic Review of Efficacy

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Teodoro del Ser[a, b] Bob Woods[e] Cornelia Beck[j] Stefanie Auer[m] Claudia Lai[n] Aimee Spector[f]
Sam Fazio[k] John Bond[g] Miia Kivipelto[o] Henry Brodaty[p] José Manuel Rojo[c] Helen Collins[h]
Linda Teri[l] Mary Mittelman[i] Martin Orrell[f] Howard H. Feldman[q, r] Ruben Muñiz[a]

Key Words
Alzheimer's disease, nonpharmacological therapy · Efficacy evaluation

Abstract
Introduction: Nonpharmacological therapies (NPTs) can improve the quality of life (QoL) of people with Alzheimer's disease (AD) and their carers. The objective of this study was to evaluate the best evidence on the effects of NPTs in AD and related disorders (ADRD) by performing a systematic review and meta-analysis of the entire field. ***Methods:*** Existing reviews and major electronic databases were searched for randomized controlled trials (RCTs). The deadline for study inclusion was September 15, 2008. Intervention categories and outcome domains were predefined by consensus. Two researchers working together detected 1,313 candidate studies of which 179 RCTs belonging to 26 intervention categories were selected. Cognitive deterioration had to be documented in all participants, and degenerative etiology (indicating dementia) had to be present or presumed in at least 80% of the subjects. Evidence tables, meta-analysis and summaries of results were elaborated by the first author and reviewed by author subgroups. Methods for rating level of evidence and grading practice recommendations were adapted from the Oxford Center for Evidence-Based Medicine. ***Results:*** Grade A treatment recommendation was achieved for institutionalization delay (multicomponent interventions for the caregiver, CG). Grade B recommendation was reached for the person with dementia (PWD) for: improvement in cognition (cognitive training, cognitive stimulation, multicomponent interventions for the PWD); activities of daily living (ADL) (ADL training, multicomponent interventions for the PWD); behavior (cognitive stimulation,

Steering Committee: J.O., B.R., L.C. and R.M.; Project Workgroup: J.O., B.R., L.C., I.C., J.P.-C., T. del S., B.W., C.B., S.A., C.L., A.S., S.F., J.B., M.K., H.B., J.M.R., H.C., L.T., M.M., M.O., H.H.F. and R.M.; principal author: J.O.

Effect of Lifestyle Activities on Alzheimer Disease Biomarkers and Cognition

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David S. Knopman, MD,[3] Rosebud O. Roberts, MBBCh,[2] Val J. Lowe, MD,[1]
Kejal Kantarci, MD,[1] Mathew L. Senjem, MS,[1] Jeffrey L. Gunter, PhD,[1]
Bradley F. Boeve, MD,[3] Ronald C. Petersen, MD, PhD,[3] and Clifford R. Jack, Jr, MD[1]

Objective: A study was undertaken to investigate the association of intellectual and physical activity with biomarkers of Alzheimer disease (AD) pathophysiology and cognition in a nondemented elderly population. The biomarkers evaluated were brain Aβ load via Pittsburgh compound B (PiB)-positron emission tomography (PET), neuronal dysfunction via ^{18}F-fluorodeoxyglucose (FDG)-PET, and neurodegeneration via structural magnetic resonance imaging (MRI).

Methods: We studied 515 nondemented (428 cognitively normal and 87 mild cognitive impairment) participants in the population-based Mayo Clinic Study of Aging who completed a 3T MRI, PET scans, and *APOE* genotype, and had lifestyle activity measures and cognition data available. The imaging measures computed were global PiB-PET uptake, and global FDG-PET and MRI based hippocampal volume. We consolidated activity variables into lifetime intellectual, current intellectual, and current physical activities. We used a global cognitive *z* score as a measure of cognition. We applied 2 independent methods—partial correlation analysis adjusted for age and gender and path analysis using structural equations—to evaluate the associations between lifestyle activities, imaging biomarkers, and global cognition.

Results: None of the lifestyle variables were correlated with the biomarkers, and the path associations between lifestyle variables and biomarkers were not significant ($p > 0.05$). Conversely, all the biomarkers were correlated with global cognitive *z* score ($p < 0.05$), and the path associations between (lifetime and current) intellectual activities and global *z* score were significant ($p < 0.01$).

Interpretation: Intellectual and physical activity lifestyle factors were not associated with AD biomarkers, but intellectual lifestyle factors explained variability in the cognitive performance in this nondemented population. This study provides evidence that lifestyle activities may delay the onset of dementia but do not significantly influence the expression of AD pathophysiology.

ANN NEUROL 2012;72:730–738

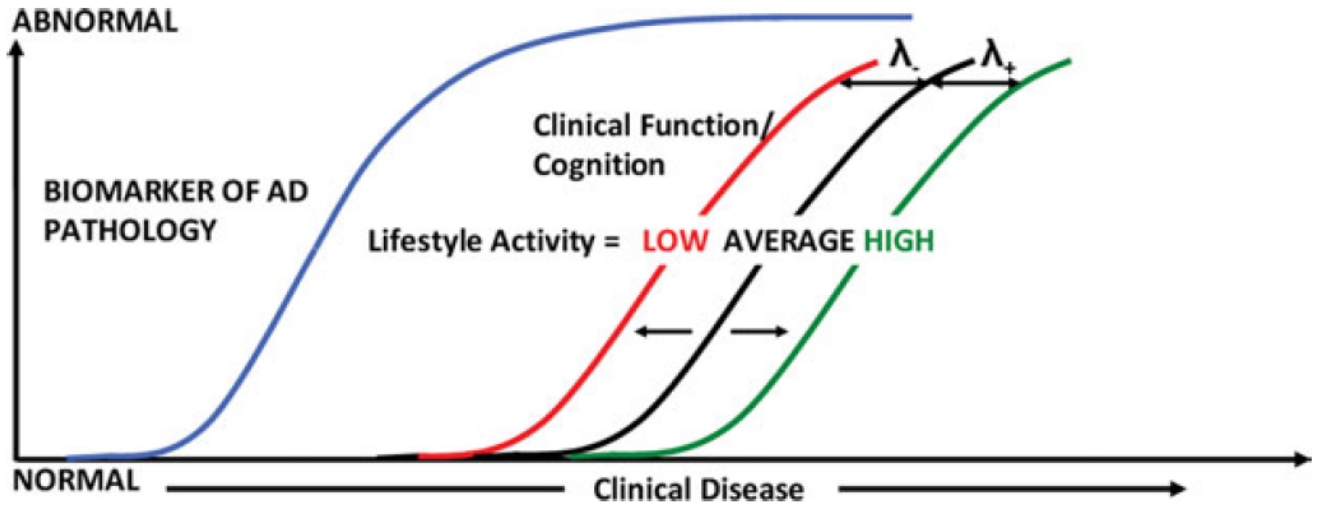


FIGURE 2: Model illustrating the effect of lifestyle activities on Alzheimer disease (AD) biomarkers and cognition or clinical function in subjects. Clinical disease stage is indicated on the horizontal axis and the magnitude of biomarker abnormalities and cognition (from normal to maximally abnormal) on the vertical axis. The cognition or clinical function curve is moved left or right based on the individual's lifestyle activity. The variable λ for lifetime intellectual activity is greater than that for current intellectual activity, and the variable λ for physical activity is close to zero.

ANN NEUROL 2012;72:730–738

Conclusion

The results of this review indicate that NPTs can make both a realistic and affordable contribution to the improvement and provision of care for people with ADRD and their CGs. In contrast to drugs, nonpharmacological interventions are often of low cost, and the cost relates to human endeavor rather than expensive technology or medication. This means that NPTs of demonstrated effectiveness might be made available cheaply in developing countries. However, it also means that for business interests there is likely to be a relative lack of return on research investment in comparison with, say, a newly licensed medication. Governments, research charities and financially strong philanthropic organizations should make significant investments in the development and dissemination of NPTs to support research to improve the evidence for their effectiveness. The benefits to PWDs, their carers and society may be great, the investments comparatively modest and potential savings for the economy may be substantial.

Olazarán J et al, Dement Geriatr Cogn Disord 30:161-178, 2010

… la lunga storia delle terapie farmacologiche

Creare le condizioni (diagnosi precoce) per arrivare alla scoperta di farmaci che agiscono nelle fasi (molto) iniziali della malattia.
Gli studi sui biomarker.

Perspective
SEPTEMBER 6, 2012

Brain Amyloid Imaging — FDA Approval of Florbetapir F18 Injection

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

N ENGL J MED 367(10):885-7, 2012

La logica di trattare in fase presintomatica per vedere se si controllano i biomarker e allo stesso tempo si allontanano i sintomi.

Stopping Alzheimer's Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms

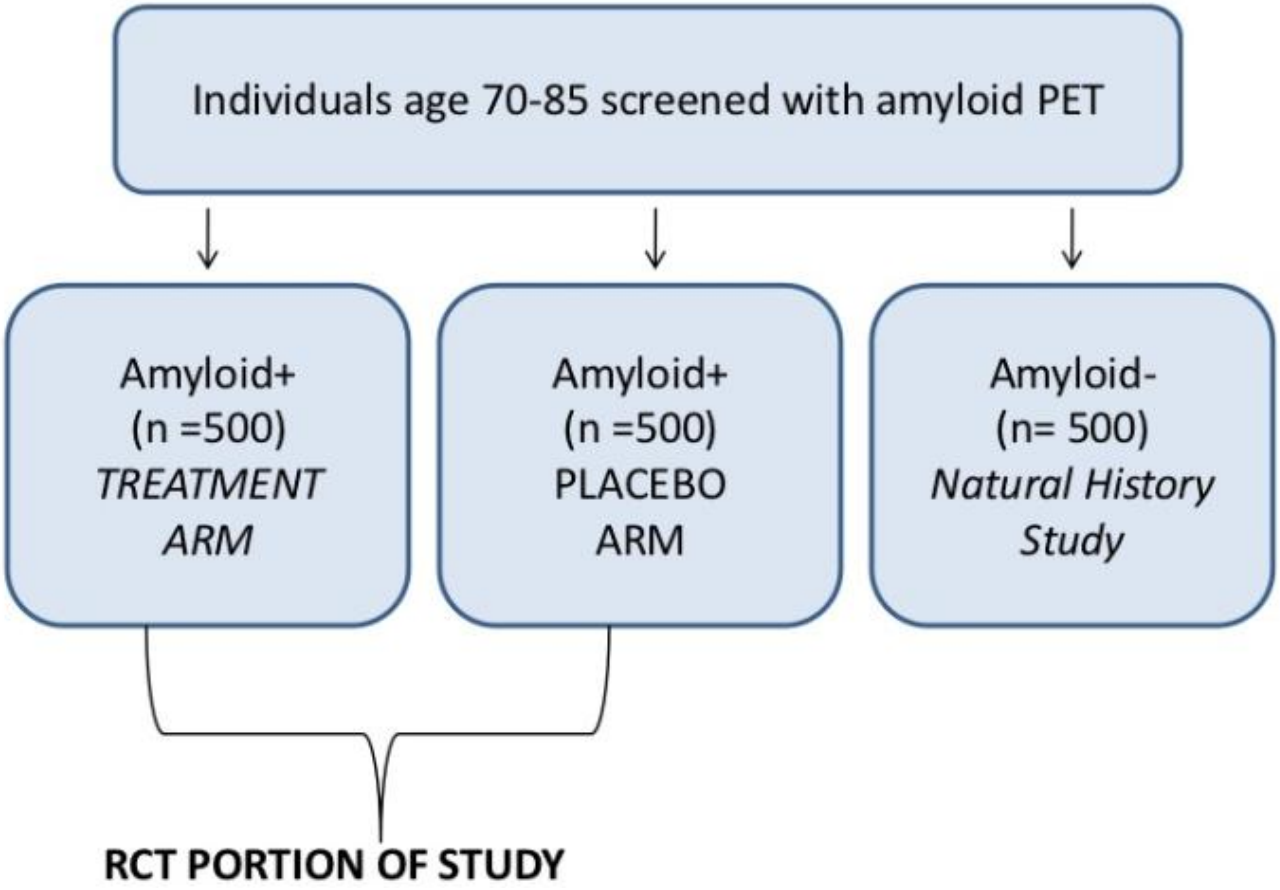
Greg Miller

Science 337:790-2, 2012

ADCS A4 Trial Design (Sperling, Aisen)
Anti-Amyloid treatment in Asymptomatic AD

- Screen cognitively normal 70+ year-olds, perhaps enriched based on subjective memory concerns, family history or cognitive tests
- Select those with amyloid in brain by PET (or LP)
- Enroll in a 3 year RCT of an anti-amyloid rx
- Primary outcome cognitive (FCSRT or other delayed recall, paragraph recall, orientation, exec fxn)
- Amyloid PET to confirm target engagement
- Biomarker profile to include CSF, structural MRI
- Other outcomes: PRO, additional cognitive tests

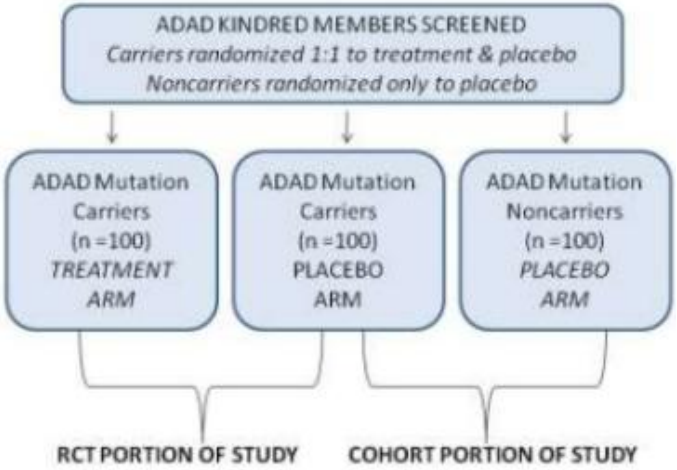
ADCS "A4" Trial of a TBN Anti-Amyloid Treatment



ALZHEIMER'S PREVENTION INITIATIVE

Alzheimer's Prevention Initiative / Genentech Treatment Trial – Colombia*

- 300 participants
  - 200 carriers, 100 noncarriers
  - Standard of care is not to disclose genetic status
- up to 18 months for enrollment
- 104-260 week trial in 200 carriers to study efficacy of treatment by comparing change in cognition and biomarkers
- Natural history ("cohort study") of 100 placebo-treated carrier & non-carriers



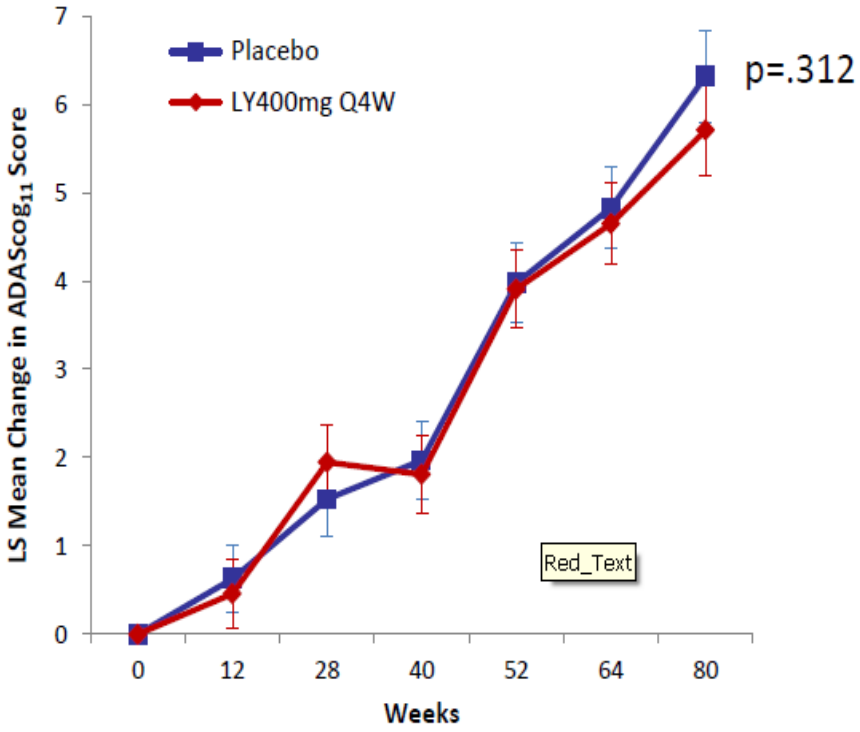
* A separate US protocol will enroll ~30 carriers and non-carriers in a similar fashion

Solanezumab EXPEDITION Trial Results

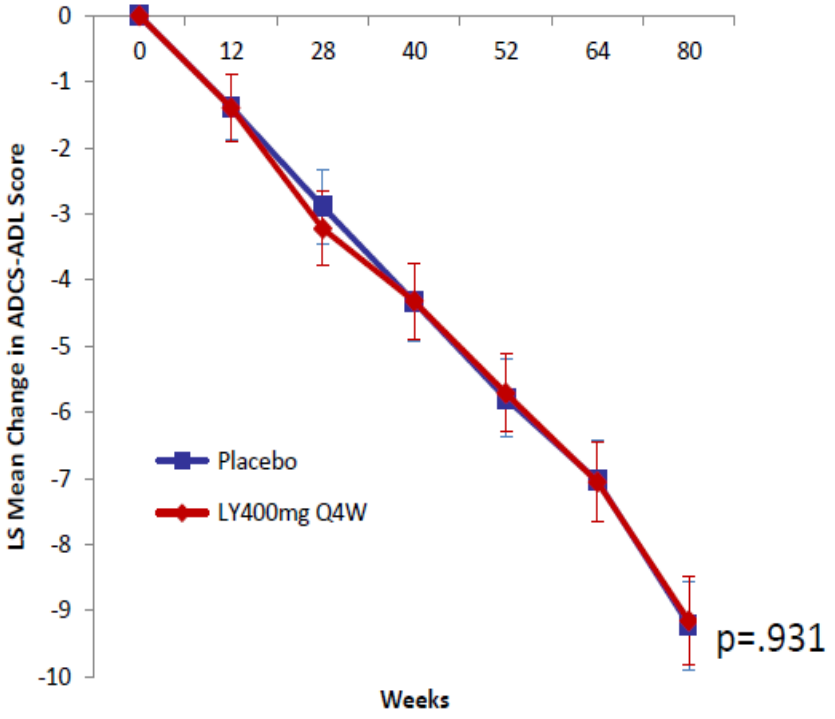
Boston, Massachusetts
October 8, 2012

Co-Primary Outcomes in Overall* Population
EXPEDITION1

Change in $ADAScog_{11}$



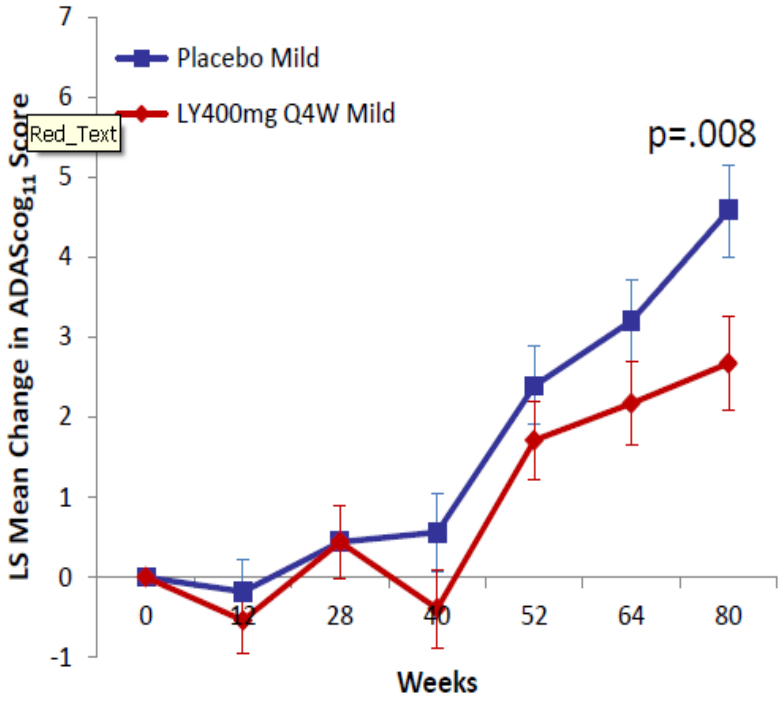
Change in ADCS-ADL



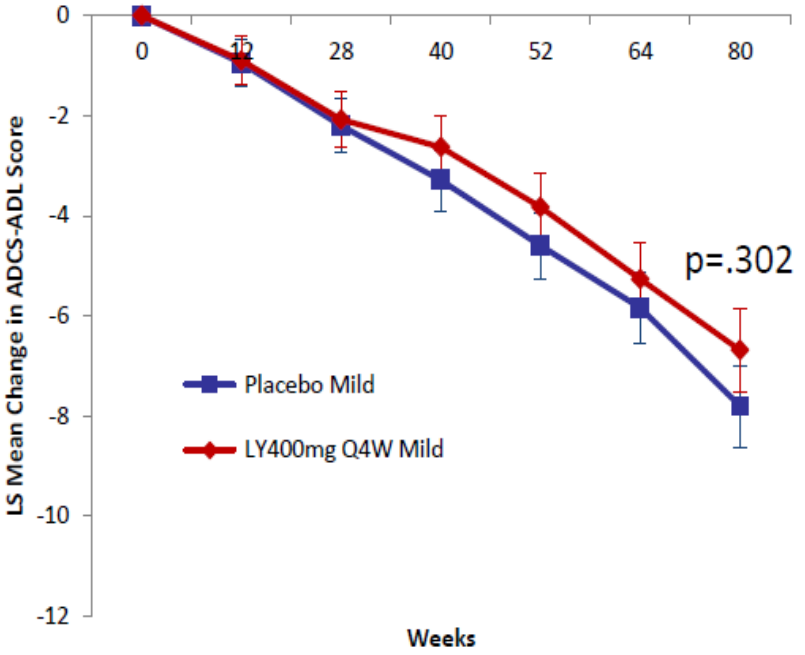
** Overall population is mild and moderate combined – MMSE 16-26 at Visit 1*

Secondary Analyses in Mild* Population
EXPEDITION1

Change in ADAScog$_{11}$

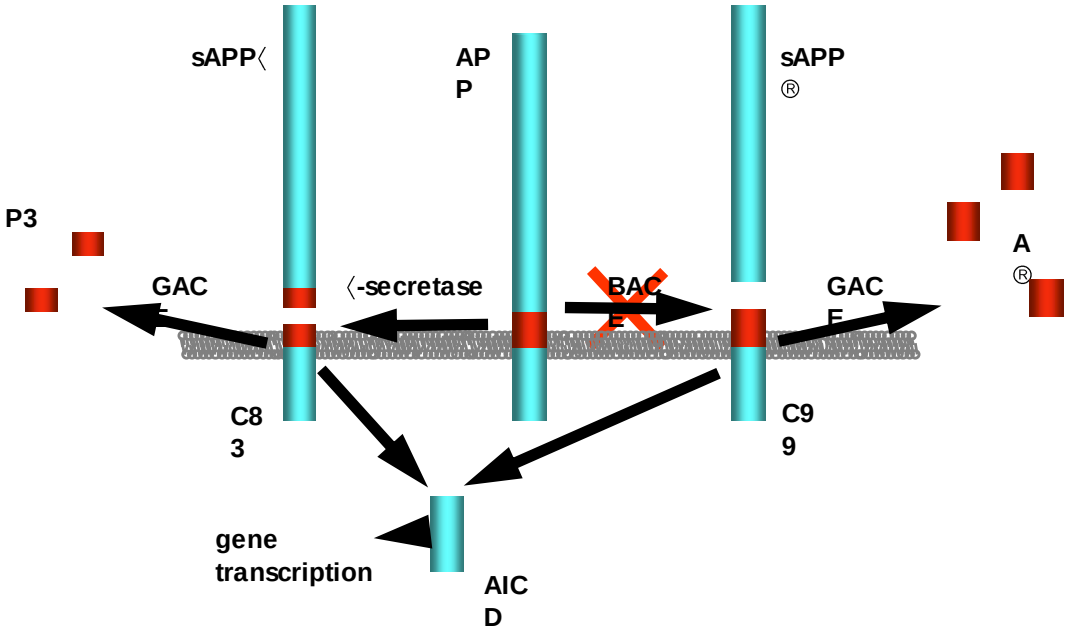


Change in ADCS-ADL



** Mild defined as MMSE 20-26 at Visit 1*

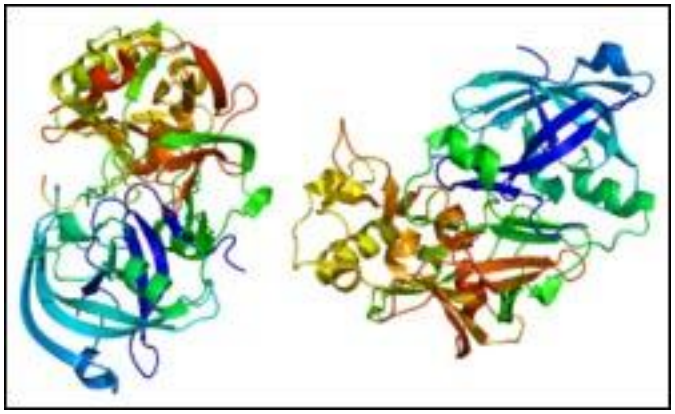
BACE inhibition is a prime target in AD



- BACE catalyzes the first step of Aβ generation (initiates β-secretory processing of APP)
- BACE blockade
  - reduces all toxic forms of APP processing: Aβ and C99
  - increases α-secretory processing considered beneficial
- Complete BACE gene knock out shows no/minor phenotype

Wave of New BACE Inhibitors Heading to Phase 2

An AAP-A673T mutation near BACE cleavage site offers a protective effect against sporadic AD



Crystal structure of BACE1, a leading target in AD drug development research

Company	Compound	Phase	Remarks
Lilly	LY2811376 & LY288721	II	failed
Eisai	E2609	I	
Merck	MK9931	I	
Roche	RG7129	I	
HPP	HPP854	I	

CAD106 summary & outlook

- ~100 AD patients have received 1-7 injections of CAD106 in completed 3 double-blind or 2 extension studies without major safety issues
- CAD106 induces an A®-specific antibody response in AD patients
- An additional ~100 mild AD patients have received 1-7 injections in the ongoing dose / regimen optimization study
  - Results from the ongoing study (including CSF biomarkers) expected early next year
- Establishing efficacy on clinical symptoms will require large studies in early stages of the disease

Table 1. Drugs with Breakthrough-Therapy Designations Announced as of September 30, 2013.*

Investigational Drug Designated as Breakthrough Therapy	Indication	Sponsor	Date Announced
Ivacaftor	Cystic fibrosis	Vertex	January 6, 2013
Ivacaftor–lumacaftor combination	Cystic fibrosis	Vertex	January 6, 2013
LDK378	Metastatic non–small-cell lung cancer	Novartis	March 15, 2013
Ibrutinib	Mantle-cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, small lymphocytic lymphoma	Pharmacyclics	April 8, 2013†
Palbociclib	Breast cancer	Pfizer	April 10, 2013
Lambrolizumab	Advanced melanoma	Merck	April 24, 2013
Daclatasvir–asunaprevir–BMS-791325 triple combination	Chronic hepatitis C	Bristol-Myers Squibb	April 25, 2013
SD-101	Epidermolysis bullosa	Scioderm	April 29, 2013
Daratumumab	Multiple myeloma	Janssen	May 1, 2013
ABT-450/r–ABT-267–ABT-333 triple combination	Genotype 1 hepatitis C	AbbVie	May 6, 2013
Obinutuzumab	Chronic lymphocytic leukemia	Genentech	May 15, 2013
Sebelipase alfa	Lysosomal acid lipase deficiency	Synageva	May 20, 2013
Asfotase alfa	Hypophosphatasia	Alexion	May 28, 2013
Serelaxin	Acute heart failure	Novartis	June 21, 2013
Drisapersen	Duchenne's muscular dystrophy	GSK	June 27, 2013
Sofosbuvir–ledipasvir combination	Hepatitis C	Gilead	July 25, 2013
Bimagrumab	Sporadic inclusion-body myositis	Novartis	August 20, 2013
Amifampridine phosphate	Lambert–Eaton myasthenic syndrome	Catalyst	August 27, 2013
Entinostat	Advanced breast cancer	Syndax	September 11, 2013
Ofatumumab	Chronic lymphocytic leukemia	Genmab and GSK	September 13, 2013
Volasertib	Acute myeloid leukemia	Boehringer Ingelheim	September 17, 2013
Alectinib	Advanced non–small-cell lung cancer	Roche	September 23, 2013

* Some sponsors do not publicly announce the receipt of a breakthrough-therapy designation.
† Multiple breakthrough-therapy designations were announced.

Sherman RE et al, N Engl J Med 369(20):1877-80, 2013

The compound strikes at a new, single target that has long flown under the radar in Alzheimer 's drug development. The target is a stress-related protein kinase, p38alpha MAPK.

"We think this protein kinase target is one of the key players in the early to mid-stage of several diseases of the central nervous system and cancer," Watterson said. Recent neuroscience research has shown that the target is activated in neurological disorders such as Alzheimer's.

These other diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), Parkinson's and frontotemporal dementia. In cancer, the protein helps malignant tumors evade the immune system as they metastasize and alter their microenvironment in a stealth type of expansion. Scientists at the University of California at San Diego currently are studying MW108 in preclinical cancer immunology research.

In a key memory experiment in the study, mice brains were injected with beta-amyloid, whose increase is one hallmark of Alzheimer's in humans. One group of mice was then administered MW108 and another group was administered a placebo.

Next, each group of mice was taught environmental cues to learn how to swim through a water maze to find a resting platform. Then the mice were placed in a different arm of the maze and tested on their ability to remember the location of the platform based on the environmental cues.

The mice administered MW108 found the resting platform in the water maze as quickly as a control group of mice. The mice given the placebo made more mistakes and took longer to find the platform. They also had difficulty learning the location of the resting platform during the teaching phase.

New Drug, Gantenerumab, Shows Early Promise Against Alzheimer's

An experimental drug showed early promise in fighting Alzheimer's. The drug, called gantenerumab, lowered levels of a toxic protein that builds up in the brains of those with the disease. Scientists hope that diminishing levels of the toxic protein, called beta-amyloid, will protect against memory loss and other symptoms of Alzheimer's.

The drug is only available for experimental use, and much more study in larger numbers of people is needed to assess its safety and effectiveness against Alzheimer's. Many medications show promise in early-stage trials but prove ineffective or too dangerous for clinical use on further testing. But the early results will lead to new studies of the drug as scientists seek ways to stem progression of the brain-ravaging illness.

For the study, researchers at three medical centers in Europe looked at 16 men and women with mild to moderate Alzheimer's disease. Some received up to seven intravenous injections of the drug every four weeks, at higher or lower doses, while others got a placebo. They also underwent specialized brain scans to assess levels of beta-amyloid in the brain.

Gantenerumab is designed to enter the brain and bind to beta-amyloid, which forms toxic clumps called plaque. Once it binds to the beta-amyloid, it is thought to cause certain cells in the brain to remove the amyloid plaques. The brain scans showed that those getting the drug had lower levels of beta-amyloid in the brain than those receiving the dummy drug.

By ALZinfo.org [1], The Alzheimer's Information Site. Reviewed by William J. Netzer [2], Ph.D., Fisher Center for Alzheimer's Research Foundation at The Rockefeller University.

Source: Susanne Ostrowitzki, Dennis Deptula, Lennart Thurfjell, et al: "Mechanism of Amyloid Removal in Paitents With Alzheimer Disease Treated With Gantenerumab." Online first, Archives of Neurology, Oct. 10, 2011.

A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Rema Raman, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Feng He, M.S., Xiaoying Sun, M.S., Ronald G. Thomas, Ph.D., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Gopalan Sethuraman, Ph.D., and Richard Mohs, Ph.D., for the Semagacestat Study Group

N Engl J Med 369(4):341-50, 2013

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by the presence of cortical amyloid-beta (Aβ) protein plaques, which result from the sequential action of β-secretase and γ-secretase on amyloid precursor protein. Semagacestat is a small-molecule γ-secretase inhibitor that was developed as a potential treatment for Alzheimer's disease.

METHODS

We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.

RESULTS

The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-cog scores worsened in all three groups (mean change, 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; P=0.15 and P=0.07, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, −9.0 points in the placebo group, −10.5 points in the 100-mg group, and −12.6 points in the 140-mg group; P=0.14 and P<0.001, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events (P<0.001 for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated.

CONCLUSIONS

As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

Outcome	Placebo	Semagacestat, 100 mg	Semagacestat, 140 mg	P Values	
				Semagacestat, 100 mg, vs. Placebo	Semagacestat, 140 mg, vs. Placebo
ADAS-cog score				0.15	0.07
No. of participants with results	486	483	497		
Mean change in score (95% CI)	6.4 (5.48 to 7.40)	7.5 (6.44 to 8.53)	7.8 (6.72 to 8.85)		
ADCS–ADL†				0.14	<0.001
No. of participants with results	480	481	490		
Mean change in score (95% CI)	−9.0 (−10.37 to −7.67)	−10.5 (−11.94 to −9.07)	−12.6 (−14.1 to −11.2)		
CDR-SB‡				0.06	<0.01
No. of participants with results	485	480	494		
Mean change in score (95% CI)	2.4 (2.06 to 2.67)	2.8 (2.47 to 3.13)	3.1 (2.73 to 3.41)		
NPI§				0.28	0.05
No. of participants with results	473	463	472		
Mean change in score (95% CI)	1.9 (0.69 to 3.12)	2.9 (1.58 to 4.21)	3.7 (2.36 to 5.08)		
MMSE				0.23	0.03
No. of participants with results	400	328	303		
Mean change in score (95% CI)	−3.4 (−3.95 to −2.86)	−3.9 (−4.51 to −3.30)	−4.3 (−4.99 to −3.68)		

* In this mixed-model repeated-measures analysis, the dependent variable was the change from the baseline score at each postbaseline visit during the initial treatment period. Fixed effects included the baseline score, treatment, MMSE score at screening, visit, treatment effect according to visit, concomitant use of an acetylcholinesterase inhibitor (usually donepezil) or memantine at baseline (yes or no), and age at baseline. Study visit was treated as a categorical variable. "Participant" was included in the model as the random effect. An unstructured covariance matrix was used to model the within-participant variance–covariance errors. The primary comparisons of interest were those of 140 mg of semagacestat versus placebo, 100 mg of semagacestat versus placebo, and 140 mg versus 100 mg of semagacestat at week 76. The numbers of participants are based on those who had a baseline score and at least one postbaseline score for each instrument. CI denotes confidence interval.

† For the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, the range is 0 to 78, and higher scores indicate better function.

‡ For the Clinical Dementia Rating–Sum of Boxes (CDR-SB), the range is 0 to 18, and higher scores indicate poorer function.

§ For the Neuropsychiatric Inventory (NPI), the range is 0 to 144, and higher scores indicate poorer function.

N Engl J Med 369(4):341-50, 2013

La mancanza di ipotesi realistiche sul mancato effetto terapeutico e sugli effetti collaterali del Semagacestat.

Il problema concettuale:
“You don’t want to rescue a liver when it is cirrosis”

In attesa del farmaco che prevenga la demenza o blocchi il meccanismo di malattia alle fasi iniziali, la ricerca clinica continua a proporre nuove alternative.
Un domani ancora incerto e le ricerche per l'oggi.

Angiotensin-Converting Enzyme Inhibitors and Alzheimer's Disease Progression in Older Adults: Results from the Réseau sur la Maladie d'Alzheimer Français Cohort

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OBJECTIVES: To assess whether angiotensin-converting enzyme inhibitor (ACE-I) treatment is associated with less cognitive decline in older adults with Alzheimer's disease (AD) than in those using other hypertensive or no drugs.

DESIGN: Four-year prospective multicenter cohort study with a biannual assessment.

SETTING: Memory clinics from 16 university hospitals in France.

PARTICIPANTS: Community-dwelling older adults with mild to moderate AD (N = 616).

MEASUREMENTS: Participants were stratified into four groups according to type and duration of antihypertensive drug treatment. Cognitive decline was assessed using the Mini-Mental State Examination (MMSE). Linear mixed-effects models were used to assess differences in decline in MMSE score between the four groups. Hypertension at each visit was included in the model.

RESULTS: Sixty-one participants had used ACE-Is continuously, 57 had used them intermittently, 189 had used other antihypertensive drugs, and 309 never used any antihypertensive drugs. Continuous ACE-Is users had a 4-year decline in MMSE of 6.4 ± 1.6 points ($P < .001$), intermittent ACE-Is users of 7.9 ± 1.1 points ($P < .001$), continuous or intermittent users of other antihypertensive drugs of 8.8 ± 0.7 points ($P < .001$), and never-users of 10.2 ± 0.6 points ($P < .001$). MMSE decline between the four groups was significantly different (adjusted $P = .02$). In subgroup analysis, the 118 (19.2%) participants who had continuously or intermittently used ACE-Is had a significant difference in 4-year MMSE decline from the 498 (80.8%) who had never used ACE-Is (7.5 ± 0.9 vs 9.7 ± 0.4; $P = .03$).

CONCLUSION: The use of ACE-Is in older adults with AD is associated with a slower rate of cognitive decline independent of hypertension. Future research is needed to explore the role of ACE-Is in long-term AD progression.

J Am Geriatr Soc 61:1482–1488, 2013.

Key words: Alzheimer's disease; older adults; angiotensin-converting enzyme-inhibitors

Statins and Cognitive Decline in Older Adults with Normal Cognition or Mild Cognitive Impairment

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OBJECTIVES: To determine the effect of statins on cognitive decline in healthy elderly adults.

DESIGN: Longitudinal.

SETTING: National Institute of Aging network of Alzheimer's Disease Centers.

PARTICIPANTS: Research volunteers with normal cognition at baseline evaluated an average 4.1 times over 3.4 years (1,244 statin users, 2,363 nonusers) and with mild cognitive impairment (MCI) at baseline evaluated an average 3.9 times over 2.8 years (763 users, 917 nonusers).

MEASUREMENTS: Cognitive performance was assessed according to 10 neuropsychological indices and the Clinical Dementia Rating Sum of Boxes (CDR-SOB). Repeated-measures analyses adjusted for age, sex, education, comorbidities, and family history of dementia were conducted.

RESULTS: Of participants with normal cognition at baseline, statin users performed significantly better across all visits in attention (Trails A) and had significantly slower annual worsening in CDR-SOB scores ($P = .006$) and slower worsening in Mini-Mental State Examination scores than nonusers (which was not significant after adjusting for multiple comparisons, $P = .05$). For participants with MCI, statin users performed significantly better across all visits on attention measures (Trail-Making Test Part A), verbal skills (Category Fluency), and executive functioning (Trail-Making Test Part B, Digit Symbol, and Digits Backward), but there were no differences in cognitive decline between users and nonusers.

CONCLUSION: Elderly adults with normal cognition at baseline who used statins had a slower rate of annual worsening in CDR-SOB than nonusers. **J Am Geriatr Soc 61:1449–1455, 2013.**

Key words: cognitive decline; statins

Nessuna “rivoluzione” nella cura delle demenze, ma molti “small gains” che migliorano la condizione del paziente e l’insieme degli approcci alla loro presa in carico.

Il “Big data approach” permetterà di fare grandi progressi?
System medicine, narrative medicine …

The Word That Shall Not Be Spoken

Thomas H. Lee, M.D.

Relief of suffering may be a task too vast to seem real for most people — something on the order of achieving "world peace" — but organizations need goals around which to build their strategies.