SPERANZE E REALTA' PER LA CURA DELL'ALZHEIMER

Brescia, 11 novembre 2016

Orazio ZANETTI

Società Italiana di Gerontologia e Geriatria- Associazione Italiana di Psicogeriatria

U.O. Alzheimer - Centro per la Memoria

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Brescia

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

SOMMARIO

- **Lo stato dell'arte**
  - **La terapia: quale spazio**
  - **Quando cominciare e quando finire**
  - **I possibili obiettivi terapeutici**
- **Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)**
- **Aspetti etici e conclusioni**

SOMMARIO

- **Lo stato dell'arte**
- **Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)**
- **Aspetti etici e conclusioni**

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Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014

Lon S. Schneider[1], **Francesca Mangialasche**[2,3], **Niels Andreasen**[4,5], **Howard Feldman**[6], **Ezio Giacobini**[7], **Roy Jones**[8], **Valentina Mantua**[9], **Patrizia Mecocci**[3], **Luca Pani**[9], **Bengt Winblad**[5], and **Miia Kivipelto**[2,5,10]

Alzheimer's disease

Philip Scheltens, Kaj Blennow, Monique M B Breteler, Bart de Strooper, Giovanni B Frisoni, Stephen Salloway, Wiesje Maria Van der Flier

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The Lancet Neurology Commission

Defeating Alzheimer's disease and other dementias: a priority for European science and society

Bengt Winblad, Philippe Amouyel, Sandrine Andrieu, Clive Ballard, Carol Brayne, Henry Brodaty, Angel Cedazo-Minguez, Bruno Dubois, David Edvardsson, Howard Feldman, Laura Fratiglioni, Giovanni B Frisoni, Serge Gauthier, Jean Georges, Caroline Graff, Khalid Iqbal, Frank Jessen, Gunilla Johansson, Linus Jönsson, Miia Kivipelto, Martin Knapp, Francesca Mangialasche, René Melis, Agneta Nordberg, Marcel Olde Rikkert, Chengxuan Qiu, Thomas P Sakmar, Philip Scheltens, Lon S Schneider, Reisa Sperling, Lars O Tjernberg, Gunhild Waldemar, Anders Wimo, Henrik Zetterberg

IL MONDO REALE
(The real world)

Gli informatori che ho incontrato negli ultimi dodici (24 ? o più ?) mesi

Citicolina (*“e le mitiche fiale da 1000 mg”*)

Omotaurina

Antiossidanti per il Cervello

XXX è un integratore alimentare particolarmente indicato quando è necessario proteggere il tessuto cerebrale dagli insulti dello stress ossidativo. XXX contiene

Carnosina, estratto di Ginkgo Biloba, vitamine del gruppo B (B1, B2, B3, B6, B9, B12), Selenio e L-cisteina,

coenzima Q10, vitamina E e β-carotene, vitamina C e flavonoidi.

glicerofosforil-etanolamina monoidrata

XXX «forte» contiene

Integratore alimentare a base di vitamina C ed E

INTEGRATORI ALIMENTARI - NUTRACEUTICI

COSTI AMPIAMENTE SUPERIORI AL DONEPEZIL

L’ultima paziente che ho incontrato (una settimana fa)

Sig.ra A.V. 76 anni, affetta da Ad (+cvd)(MMSE: 22/30)
Malgrado la raccomandazione di usare un antiaggregante in passato, preferisce il Gingko biloba

Un figlio, veterinario sta applicando l’ozonoterapia negli allevamenti di animali

Lei stessa si sta sottoponendo a “sedute” di ossigeno-ozono terapia (auto-emoinfusione)

The Reappearance of Procaine Hydrochloride (Gerovital H3) for Antiaging

Thomas Perls, MD, MPH
Section of Geriatrics, Department of Medicine, School of Medicine, Boston University, Boston Medical Center, Boston, Massachusetts

BREAKING NEWS

The Reappearance of Procaine Hydrochloride (Gerovital H3) for Antiaging

Thomas Perls, MD, MPH
Section of Geriatrics, Department of Medicine, School of Medicine, Boston University, Boston Medical Center, Boston, Massachusetts

JAGS 61:1024–1025, 2013

2013 !

Phenomenal improvement in the psychic, physiological, and social functioning of 189 elderly subjects who had undergone procaine (Novocaine) therapy over a period of ten years. Patients bedridden with arthritis and rheumatism were mobile again, living normal lives; hypertension and angina pectoris vanished. Severely disoriented psychiatric patients recovered; memory, concentration and perception were restored; extrapyramidal rigidity in Parkinson's disease diminished. Hair growth was stimulated, repigmentation of gray hair occurred in some cases, flaccid senile skin regained its turgor and became tight and smooth, the subjects looked ten years younger. A notable reduction in mortality rates were also reported.[5]

Aslan, 1973


Cholinergic hypothesis
1982
AchE inhibitors
1993
Donepezil
1997
Memantine
2009

	Data commercializzazione	
	USA	Italia
Tacrina	1993	-
Donepezil	1997	1998
Rivastigmina	1998	1999
Galantamina	2000	2002
Memantina		2005

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

N Engl J Med 2010;362:2194-201.

Early Alzheimer's Disease

Richard Mayeux, M.D.

Table 1. Drug Therapy for Alzheimer's Disease.

Medication	Dose	Common Adverse Side Effects	Comments
Donepezil (Aricept)	5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams	Available in a single daily dose
Rivastigmine (Exelon)	3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a maximum daily dose of 12 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, indigestion, dizziness, drowsiness, headache, diaphoresis, weakness	Available as a patch
Galantamine (Razadyne)	8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue	Available as an extended-release capsule
Memantine (Namenda)	5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg	Constipation, dizziness, headache, pain (nonspecific)	Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease

NICE technology appraisal guidance 217

Issue date: March 2011

Review date: April 2014

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease

Review of NICE technology appraisal guidance 111

NOTE: This guidance replaces NICE technology appraisal guidance 111 issued in November 2006 (amended September 2007, August 2009).

The review and re-appraisal of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease has resulted in a change in the guidance. Specifically:

- donepezil, galantamine and rivastigmine are now recommended as options for managing mild as well as moderate Alzheimer's disease, **and**
- memantine is now recommended as an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and as an option for managing severe Alzheimer's disease.

Appraisal: A decision-making process

Option: One of the choices which can be made

1 Guidance

1.1 The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 1.3 and 1.4.

1.3 Treatment should be under the following conditions:

- Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.
- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
- Patients who continue on treatment should be reviewed regularly using cognitive, global, functional and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. Carers' views on the patient's condition at follow-up should be sought.

1.2 Memantine is recommended as an option for managing Alzheimer's disease for people with:

- moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors **or**
- severe Alzheimer's disease.

Treatment should be under the conditions specified in 1.3.

Mini Mental State Examination (MMSE) score:

- mild Alzheimer's disease: MMSE 21–26
- moderate Alzheimer's disease: MMSE 10–20
- moderately severe Alzheimer's disease: MMSE 10–14
- severe Alzheimer's disease: MMSE less than 10.

2.7 The aims of treatment are to promote independence, maintain function and treat symptoms including cognitive, non-cognitive (hallucinations, delusions, anxiety, marked agitation and associated aggressive behaviour), behavioural and psychological symptoms.

4.3.14 The Committee considered the clinical effectiveness of memantine as an adjunct to AChE inhibitor treatment. The Committee noted evidence that showed no statistically significant benefit for combination treatment with memantine and AChE inhibitors for cognitive, functional, behavioural or global outcomes. The Committee was also made aware of ongoing trials for combination therapy including the DOMINO-AD (donepezil and memantine in moderate to severe Alzheimer's disease) study. The Committee concluded that combination treatment with memantine and AChE inhibitors could not be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy.

ALLEGATO 1

Nota 85

Inibitori dell'acetil-colinesterasi: **– donepezil** **– galantamina** **– rivastigmina** **– memantina**	**La prescrizione a carico del SSN, su diagnosi e piano terapeutico delle Unità di Valutazione Alzheimer (UVA) individuate dalle Regioni e dalle Provincie Autonome di Trento e Bolzano, è limitata ai pazienti con malattia di Alzheimer di grado lieve, con MMSE tra 21 e 26 (donepezil, rivastigmina, galantamina) o moderato, con MMSE tra 10 e 20 (donepezil, rivastigmina, galantamina, memantina).** Alle UVA è affidato il compito di effettuare o, eventualmente, confermare una diagnosi precedente e di stabilire il grado di severità in accordo alla scala MMSE. Il piano terapeutico deve essere formulato sulla base della diagnosi iniziale di probabile demenza di Alzheimer di grado lieve-moderato. La risposta clinica dovrà essere monitorata ad intervalli regolari dall'inizio della terapia: • a 1 mese, per la valutazione degli effetti collaterali e per l'aggiustamento del piano terapeutico; • a 3 mesi, per una prima valutazione della risposta e per il monitoraggio della tollerabilità; la rimborsabilità del trattamento oltre i tre mesi deve basarsi sul non peggioramento dello stato cognitivo del paziente valutato tramite MMSE ed esame clinico; • ogni 6 mesi per successive valutazioni della risposta e della tollerabilità.

Original Paper

Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology

Psychopharm

Journal of Psychopharmacology
0(0) 1–23

DOI: 10.1177/0269881110387547
jop.sagepub.com
SAGE

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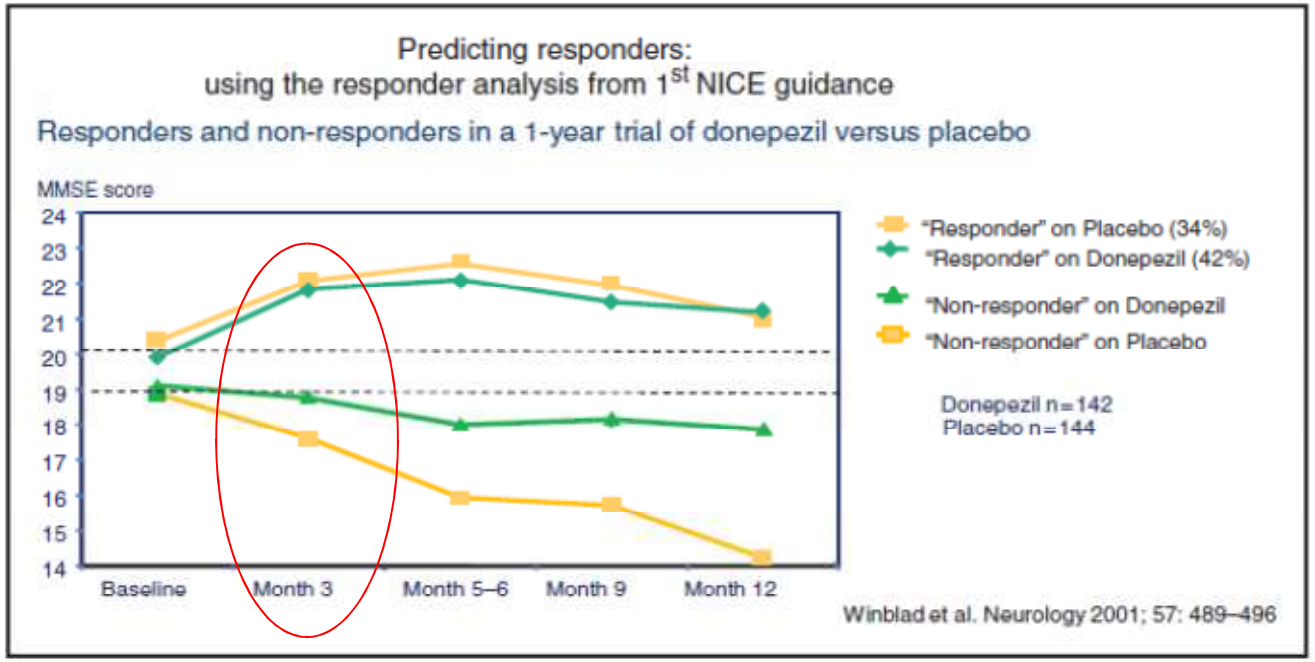
Gordon Wilcock, Professor of Clinical Geratology, University of Oxford, UK
David Wilkinson, Consultant in Old Age Psychiatry, Southampton, UK

J.of Psychopharmacology
2011;25:997-1019

Table 3. Summary box: Alzheimer's disease

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and memantine	There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease and type I evidence for memantine in moderate to severe Alzheimer's disease.	A
Switching between cholinesterase inhibitors	There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.	B
Combination therapy	There is type II evidence for adding memantine to a cholinesterase inhibitor, but also a negative type 1b study. Until further studies are available the benefits of combination therapy is unclear.	B

O'Brien &
Burns 2010



O'Brien & Burns 2010

Table 4. Summary box: Dementia with Lewy bodies

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type I evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia and that both cognitive and neuropsychiatric symptoms improve.	A
	There is type II evidence to support equal efficacy of all three cholinesterase inhibitors.	B
Memantine	There is type II evidence that memantine may produce cognitive and global improvements.	B

Table 5. Summary box: Vascular dementia

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and memantine	There is type I evidence showing small cognitive improvements with both cholinesterase inhibitors and memantine in vascular dementia. However, benefits in terms of global outcome are not seen and adverse events for cholinesterase inhibitors (but not memantine) are significantly greater than placebo. Evidence indicates that neither cholinesterase inhibitors nor memantine should be prescribed to people with vascular dementia, though those with mixed VaD and Alzheimer's disease may benefit.	A

O'Brien &
Burns 2010

Table 6. Summary box: Frontotemporal dementia

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type I evidence that cholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia.	A
SSRIs	There is type II evidence that SSRIs may help some behavioural aspects of frontotemporal dementia, but do not improve cognition. Studies are mixed and further evidence is needed.	B

Table 7. Summary box: Progressive supranuclear palsy

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type II evidence that cholinesterase inhibitors are not helpful in progressive supranuclear palsy. No treatments can be recommended at the current time.	B

O'Brien &
Burns 2010

1. Neurocase. 2012 Apr 19.

A case of apathy due to frontotemporal dementia responsive to memantine.

Links KA, Black SE, Graff-Guerrero A, Wilson AA, Houle S, Pollock BG, Chow TW.

Results: Informants reported reduction of the apathy. The insula and cerebellum, showed improved metabolism.

Conclusion: Further study to correlate the effects of memantine on apathy are warranted.

Table 8. Summary box: Mild cognitive impairment

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and vitamin E	There is type I evidence that cholinesterase inhibitors are not effective in reducing the risk of developing Alzheimer's disease and type I evidence that vitamin E is not effective in reducing the risk of Alzheimer's disease.	A

O'Brien &
Burns 2010

Table 10. Summary box: Other treatments for dementia

Intervention	Level of evidence	Recommendation
Dimebon for AD	There is preliminary level II evidence of a benefit of dimebon in AD, but further studies are awaited. Dimebon should not be prescribed for AD until further studies report.	B
Gingko biloba for dementia	There is level I evidence that Gingko biloba is not beneficial in improving cognitive symptoms in dementia.	A
Gingko biloba for prevention of dementia	There is level I evidence that Gingko biloba is not effective in the primary prevention of either all-cause dementia or Alzheimer's disease.	A
Hormone Replacement Therapy (HRT) in prevention and treatment of Alzheimer's disease in post-menopausal women	There is level I evidence that HRT is not effective either in treating cognition in Alzheimer's disease, or for the primary prevention of all-cause dementia or Alzheimer's disease.	A
	There is level I evidence that HRT is harmful. HRT should not be prescribed either as a prevention or treatment for dementia, including Alzheimer's disease.	A
Folate and vitamin B12 for dementia	There is type I evidence that supplementation with folic acid with or without vitamin B12 does not benefit cognition in people with dementia. On current evidence, neither vitamin B12 nor folate, either singly or in combination, can be recommended as treatments for dementia, or for dementia prevention.	A
Statins for the treatment or prevention of dementia	There is level I evidence that statins do not prevent dementia.	A
	There is level II evidence that statins do not produce cognitive benefits in AD.	B

O'Brien &
Burns 2010

Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2012;34:167–173
DOI: 10.1159/000342927

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Published online: October 5, 2012

Response to Rivastigmine Transdermal Patch or Memantine plus Rivastigmine Patch is affected by Apolipoprotein E Genotype in Alzheimer Patients

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Hae Ri Na[g] Soo Jin Yoon[h] Hyun Young Park[i] Joon Hyun Shin[j] Soo-Jin Cho[j]
Hyon-Ah Yi[k] Mun Seong Choi[l] Jae-Hyeok Heo[f] Kyung Won Park[m]
Kwang K. Kim[b] Seong Hye Choi[n]

tients with moderately severe AD (MMSE ≤15) who were APOE ε4 carriers showed higher responder rates on ADCS-ADL with memantine plus rivastigmine patch compared to rivastigmine patch monotherapy. ***Conclusion:*** Moderately severe AD patients with the APOE ε4 allele may respond more favorably to memantine plus rivastigmine patch than ε4 noncarriers.

QUALE OUTCOME ?

Alzheimer Disease and Associated Disorders
Vol. 11, Suppl. 6, pp. 12–17

Which Outcomes Matter in Alzheimer Disease and Who Should Define Them?

Robert L. Kane

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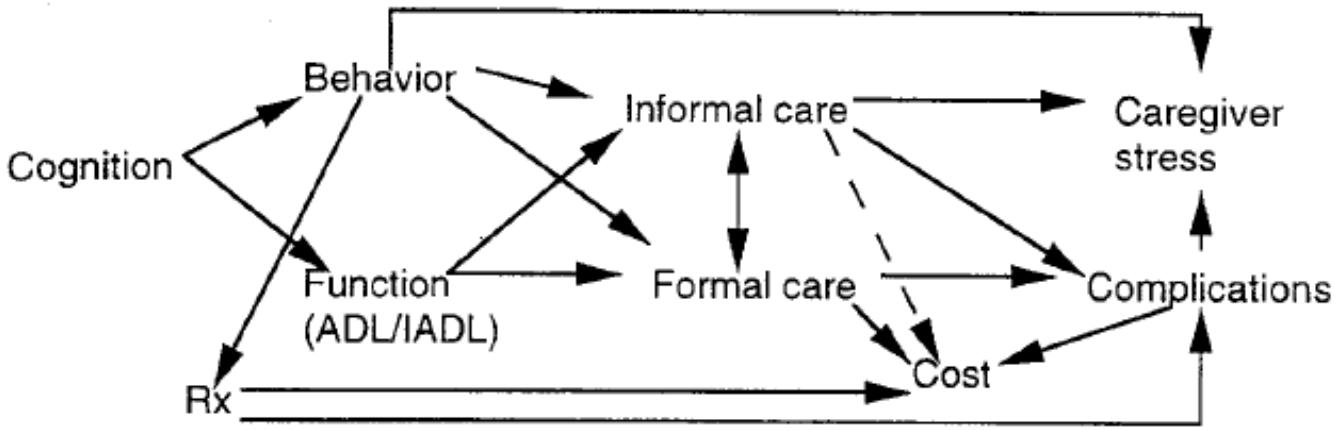
OUTCOMES IN ALZHEIMER DISEASE



SOMMARIO

- Lo stato dell’arte
- **Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)**
- Aspetti etici e conclusioni

Alzheimer's disease: clinical trials and drug development

Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto

Alzheimer's disease is the most common cause of dementia in elderly people. Research into Alzheimer's disease therapy has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of Alzheimer's disease and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials. Many clinical and experimental studies are ongoing, but we need to acknowledge that a single cure for Alzheimer's disease is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered. Preclinical research is constantly providing us with new information on pieces of the complex Alzheimer's disease puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. Several promising randomised controlled trials are ongoing, and the increased collaboration between pharmaceutical companies, basic researchers, and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of Alzheimer's disease.

Lancet Neurol 2010; 9: 702–16

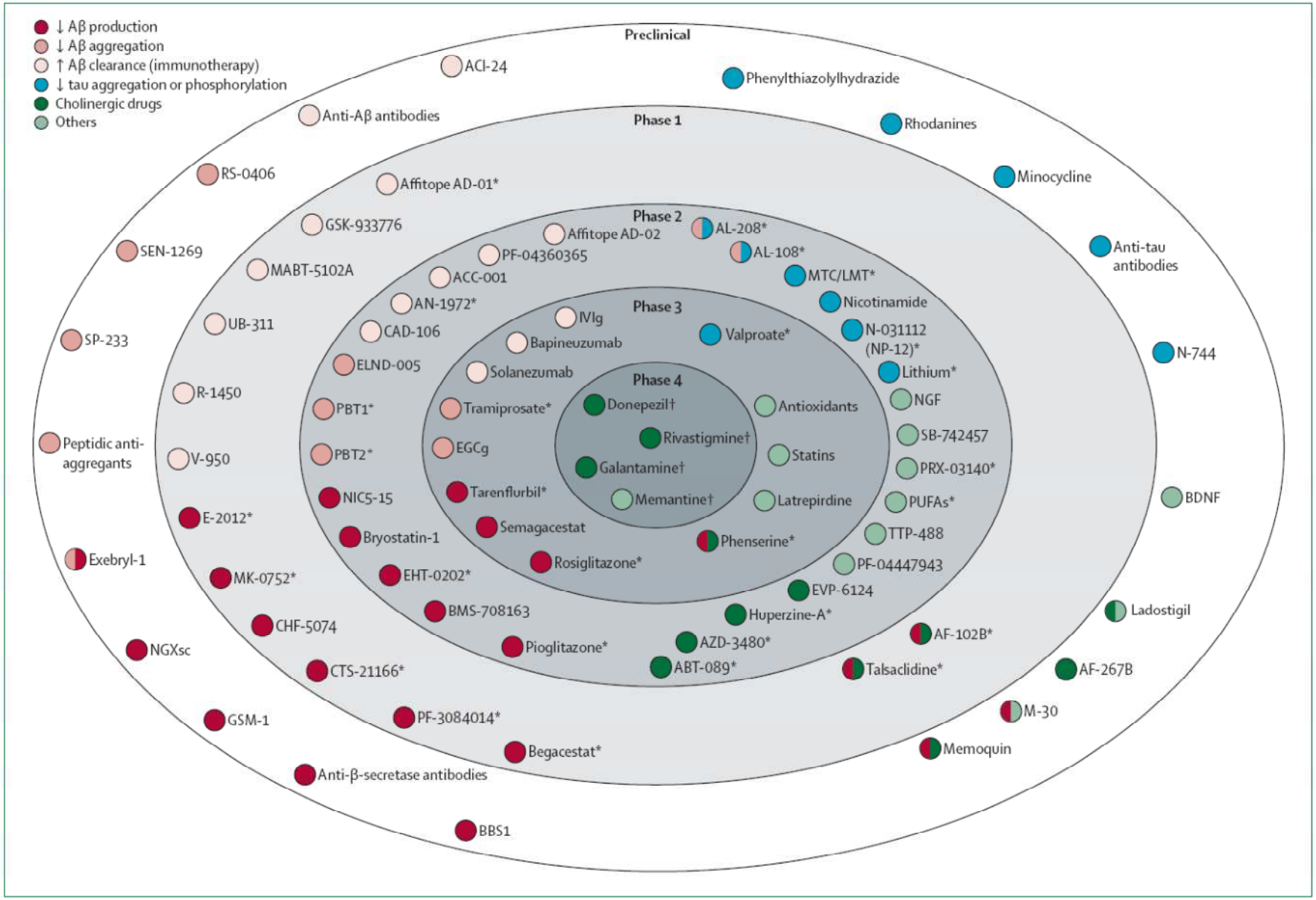


Figure: **Drug development in Alzheimer's disease**

Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

The Journal of Nutrition, Health & Aging©
Volume 14, Number 4, 2010

JNHA: CLINICAL TRIALS AND AGING

THE POTENTIAL AND LIMITS FOR CLINICAL TRIALS FOR EARLY ALZHEIMER'S DISEASE AND SOME RECOMMENDATIONS

L.S. SCHNEIDER

Table 2
Model criteria and methods for phase II drug development trials for early or prodromal AD

Characteristic	Recommendation	Rationale
Experimental intervention (e.g., drug, antibody, psychotherapeutic, environmental)	Appropriate for MCI, early AD, and non-dementia patients who may not progress or may improve in their symptoms	Expect effectiveness over brief period, should be substantially safe considering participants have few symptoms, slow progression
Participant inclusion criteria	Episodic memory impairment as described (6), repeated memory assessments over several weeks. Trial should include biomarkers as stratification variables.	The need to rely on episodic memory impairment makes diagnosis dependent on actuarial tests. Repeated testing is needed to gain reliability in the diagnosis.
Exclusion criteria	Impairment in activities of daily living or dementia	Without these or similar criteria many would fulfill criteria for probable AD. Operationalization may be difficult
Methods	Multicenter, randomized, double-blinded, placebo-controlled trial. Randomization may be stratified by biomarker or cognitive severity	Needed to control for various known and unknown sources of bias
Durations	Based on expected drug actions. Brief for symptomatic effects, over 2 years for attenuation of progression	Patients with early AD are likely to show less change over time than mild AD patients
Primary outcome	Cognitive outcomes emphasizing memory function, different from tests used for early AD diagnosis	Early AD primarily defined by episodic memory impairment in the absence of many other symptoms
Secondary Outcome	CGIC, self-, informant- and clinician-rated, health-related QoL	Because ADLs are not likely to be impaired, and patients and informants notice impairment, self- and observer-rated global assessments and health-related QoL ratings are needed to assess further clinical significance
Statistics	Analysis based on stratification, repeated assessments of cognitive change over course of trial.	Assess outcomes based on biomarker status; repeated measures of cognitive outcomes to enhance precision and describe treatment effects

Ushering in the study and treatment of preclinical Alzheimer disease

Jessica B. Langbaum, Adam S. Fleisher, Kewei Chen, Napatkamon Ayutyanont, Francisco Lopera, Yakeel T. Quiroz, Richard J. Caselli, Pierre N. Tariot and Eric M. Reiman

Langbaum, J. B. *et al. Nat. Rev. Neurol.* 9, 371–381 (2013); published online 11 June 2013; corrected online 16 July 2013; doi:10.1038/nrneurol.2013.107

Key points

- The pathogenic cascade of Alzheimer disease (AD) is thought to begin at least one to two decades prior to cognitive impairment
- Disappointing results of several AD drugs in late-stage trials have suggested the need for early therapeutic intervention, calling for development of biomarkers and sensitive cognitive measures of preclinical disease
- The best established measurements for detection and tracking of preclinical and clinical AD include MRI, fluorodeoxyglucose PET, amyloid PET, and cerebrospinal fluid measures of amyloid-β_{42}, total tau, and phospho-tau
- Studies of individuals with inherited AD can provide insights into cognitive and biomarker changes that precede clinical manifestation of AD, and are suitable candidates for ongoing monitoring and early-intervention strategies
- We are entering an era of AD prevention research, with a number of preclinical AD treatment trials in the planning stages or under way for several at-risk, cognitively unimpaired populations

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Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014

Lon S. Schneider[1], **Francesca Mangialasche**[2,3], **Niels Andreasen**[4,5], **Howard Feldman**[6], **Ezio Giacobini**[7], **Roy Jones**[8], **Valentina Mantua**[9], **Patrizia Mecocci**[3], **Luca Pani**[9], **Bengt Winblad**[5], and **Miia Kivipelto**[2,5,10]

Mild cognitive impairment trials (approximately 2000–2005)

in cognitive rating scales. The drugs investigated included the marketed agents rivastigmine, galantamine, donepezil, vitamin E, vitamin B complex and rofecoxib [66–70]. The nootropic piracetam was used in a small 1-year MCI pilot trial [71] and donepezil in larger 6-month [72] and 12-month trials [73].

The results of all the trials in MCI were negative, with no significant benefit on progression or onset of Alzheimer's disease dementia. The rates of progression from MCI to

As with the 12-month trials, anti-inflammatory and neuroprotective agents were initially tested in 18-month trials of hydroychloroquine [77], the cholesterol-reducing 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors atorvastatin [78] and simvastatin [79], food supplements such as vitamin B combinations to lower homocysteine [80] and docosahexaenoic acid [81]. Except for two very large phase 3 trials with the neuroprotective 5-HT_{1A} agonist xaliproden [82], the early 18-month trials investigated marketed drugs or available food supplements. More recent phase 2 and 3 trials involved almost entirely investigational drugs to test the amyloid hypothesis. These included an Aβ aggregation inhibitor tramiprosate [83], two phase 3 trials of a gamma-secretase modulator to lower Aβ levels, tarenflurbil [84], the Aβ aggregation inhibitor scyllo-inositol (ELND005) [85], two trials of the gamma-secretase inhibitors semagacestat [86]and one of avagacestat [87], a RAGE inhibitor (PF 04494700 or TTP 488), infusions of Aβ antibodies including phase 2 and 3 trials of bapineuzumab [88] [unpublished], two phase 3 trials of solanezumab [unpublished], and immunoglobulin G (IVIG) [unpublished]. All these trials yielded null results with respect to their main outcomes. Other 18-month trials are ongoing.

Prodromal Alzheimer's disease trials (approximately 2010–2014)

The earlier MCI trials used slightly differing definitions for MCI, including amnestic MCI in one trial [66] which later became 'MCI due to Alzheimer's disease' for the Alzheimer Disease Neuroimaging Initiative and for the new research diagnostic guidelines for Alzheimer's disease in 2011 [93]. The advancement of trials for prodromal Alzheimer's disease followed proposed research criteria from an international workgroup [94], i.e. with the intent to diagnose Alzheimer's disease before dementia onset, and to enrich clinical trial samples in terms of increasing confidence that patients actually had Alzheimer's disease pathology and presumably would advance to dementia after a relatively brief interval [95]. The inclusion of patients with prodromal disease also allows individuals to be treated earlier in their illness and, hypothetically, at a time when some drugs may be more effective than they would be at a later stage.

The current 'MCI due to Alzheimer's disease' and prodromal Alzheimer's disease trials have characteristics similar to the 18-month trials described above and include a requirement that participants have positive Aβ biomarkers, such as low CSF Aβ42 concentrations or increased retention of an Aβ-binding ligand on amyloid PET scan, in order to enhance the likelihood that participants have Alzheimer's disease pathology. These trials are different from previous MCI trials in having somewhat shorter treatment periods of 18 to 24 months and in the use of biomarkers both for entry criteria and as indices of change that might be

Prevention trials (approximately 1996–2014)

Recent advances in prevention trials include enrolling elderly people with an increased risk of Alzheimer's disease based on a biomarker or genetic marker, and the use of multi-domain interventions composed of concurrent management of risk factors based on lifestyle changes and marketed pharmacological products. The trials include the Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability (FINGER), Multi-domain Alzheimer Prevention Study (MAPT) and Prevention of Dementia by Intensive Vascular Care (PreDIVA) [105]. Additionally, there are a number of planned trials involving structured physical activity interventions that are discussed elsewhere in this issue [105].

The current, single-drug, pharmaceutical company-sponsored prevention trials are components of proprietary drug development programmes in which participants must have an Aβ biomarker as an enrichment or risk factor, or a genetic risk marker or specific *PSEN 1* or *APP* mutation that determines their eligibility. These studies include the Alzheimer's Prevention Initiative (API), the Dominantly Inherited Alzheimer Network (DIAN), the Anti-amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) and the ApoE/TOMM40 trials; the first three tested Aβ antibodies and the latter a very low-dose of the thiazolidinedione pioglitazone [105].

The two trials in patients with autosomal dominantly inherited Alzheimer's disease are unique in that there is no question that all participants will develop cognitive and neurological impairment and will have Alzheimer's disease pathology. As participants are symptom free, they can be considered to have preclinical Alzheimer's disease. Both trials are investigating the efficacy of Aβ antibodies – crenezumab in the API and gantenerumab and solanezumab in the DIAN study – and so are also tests of the amyloid hypothesis. One consideration is that Aβ42-reducing approaches may have a particular effect in familial Alzheimer's disease where Aβ42 formation is increased, compared to sporadic Alzheimer's disease where Aβ42 formation is not affected. The A4 trial is testing the concept of treating participants who are amyloid PET positive, without notable cognitive symptoms (i.e. who are at statistical risk of sporadic, late-onset Alzheimer's disease), with the Aβ antibody solanezumab.

The pioglitazone trial is also unique in that it includes approximately 5000 non-cognitively impaired participants whose increased risk of Alzheimer's disease is determined by a biomarker comprising age, particular variants of the *TOMM40* gene and *APOE* genotypes; the efficacy of low dose pioglitazone to delay the onset of MCI due to Alzheimer's disease will be evaluated over the course of 6 years in the high-risk biomarker group.

The evolution of pharmacological targets and the new symptomatic phase (approximately 2007–2014)

The amyloid cascade hypothesis [19] has dominated drug development for the past two decades. Targets were developed for individual steps in the cascade: secretase inhibitors and modulators, passive and active immunization with antibodies against various epitopes of Aβ monomers, oligomers and fibrils, fibrilization inhibitors, anti-aggregants and other approaches. As a result of recent development failures the currently active phase 2 and 3 anti-amyloid approaches involve three antibodies with an emphasis on mild, prodromal and preclinical Alzheimer's disease; Aβ vaccines, and beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) or β-secretase inhibitors. There are several examples of vaccines in development, including CAD-106, ACC-001, V950, AC-24, AD01 and AD02, all composed of peptides or fragments that mimic $A\beta_{42}$.

The BACE-1 competitive inhibitor MK-8931 is being assessed in prodromal and mild to moderate Alzheimer's disease populations in two phase 2 trials for 2 years and 18 months, respectively, with the latter enrolling over 1900 patients (NCT01739348). Other BACE-1 inhibitors are in development, although there have been failures due to toxicity.

Interest in tau-based approaches has led to putative inhibitors of enzymes involved in tau phosphorylation (e.g. GSK-3β), aggregation inhibitors, microtubule stabilizers and inhibitors of tau N-glcNAcylation. Agents in development include small molecules, monoclonal antibodies and vaccines. Most advanced is a formulation of methylene blue, methylthioninium chloride, (TRx0237) (TauRx), that may act as a tau aggregation inhibitor.

In summary, anti-amyloid and tau-based approaches are being advanced in 18-month trials in patients with mild and prodromal Alzheimer's disease, and small molecule, cholinergic approaches are entering phase 3 in 6-month trials in patients with mild to moderate dementia. The cholinergic approaches are better supported by 'proof of concept' trials and appear to improve clinical outcomes.

done is correct. The lack of progress despite substantial effort may rest, as stated by Leber, a former FDA director, 'Not in our methods, but in our ignorance' [129].

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Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014

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	Manufacturer	Epitope	Origin	Isotype	Target	Possible mechanism of action	Outcomes in latest stage trial	Amyloid biomarker inclusion criteria in trials	Trials planned or in progress	Rate of amyloid-related imaging abnormalities
Solanezumab (NCT0760005, NCT01900665)	Eli Lilly	Mid-domain	Humanised	IgG1	Soluble, monomeric, non-fibrillar Aβ	Sequestration of soluble monomeric Aβ	Negative clinical outcomes in two phase 3 trials in mild-to-moderate Alzheimer's disease; possible slowing of cognitive decline in mild disease	None	Phase 3 trials underway in mild, preclinical, and autosomal-dominant Alzheimer's disease	Low
Bapineuzumab (NCT00575055, NCT00574132)	Pfizer/Johnson & Johnson	N-terminus	Humanised	IgG1	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in two phase 3 trials despite significant decrease in amyloid PET and phosphorylated tau concentrations in cerebrospinal fluid	None	–	Related to dose and *APOE* ε4 carrier status
Crenezumab (NCT 01397378, NCT01723826, NCT01998891)	Roche/ Genentech	Mid-domain	Humanised	IgG4	All forms of Aβ (fibrillar, oligomeric, monomeric)	Microglia-mediated clearance	Negative clinical outcomes in phase 2 trials in mild-to-moderate Alzheimer's disease; possible cognitive slowing in mild disease in patients given high doses	None in ABBY trial; amyloid PET in BLAZE trial	Phase 3 trial in autosomal-dominant Alzheimer's disease underway	Low
BAN2401 (NCT01767311)	Eisai/Biogen	N-terminus	Humanised	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	No phase 2 trials yet completed	Amyloid PET	Phase 2 trial underway in mild cognitive impairment	–
Gantenerumab (NCT01224106, NCT02051608)	Roche/ Genentech	N-terminus and mid-domain	Human (phage display library and affinity maturation)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Negative clinical outcomes in phase 3 trial for prodromal Alzheimer's disease	Cerebrospinal fluid Aβ	New phase 3 trial in planning phase	Related to dose and *APOE* ε4 carrier status
Aducanumab (NCT02484547, NCT02477800)	Biogen/ Neurimmune	N-terminus	Human (RTM)	IgG1	Fibrillar and oligomeric Aβ	Microglia-mediated clearance	Dose-dependent decrease in amyloid PET and cognitive decline in early Alzheimer's disease (mild cognitive impairment and mild disease) in interim analysis of phase 1b trial	Amyloid PET	Phase 1 trial in prodromal or mild Alzheimer's disease and phase 3 trial of early disease underway	Related to dose and *APOE* ε4 carrier status

Aβ=amyloid β. –=not applicable. RTM=reverse translational medicine.

Table: **Anti-amyloid monoclonal antibodies in clinical development**

considerations.[142] If results suggest Alzheimer's disease, the patient might be put on a cocktail of anti-amyloid compounds, anti-tau drugs, synaptic enhancers, repurposed drugs producing small epigenetic changes, and perhaps even gene therapy directed at *APOE4*, and progression to dementia would be monitored. Imaging

If progress accelerates as expected, a patient with early symptoms of Alzheimer's disease in 2025 will be treated substantially differently from how they are now (panel 3). They will probably be seen by their primary care doctor in most countries upon first complaints. This doctor will prescribe risk-factor management, treat comorbid disease, and provide personalised advice for lifestyle modification. The patient will also be referred to a specialist and undergo MRI, amyloid and tau imaging, or measurement of cerebrospinal fluid biomarkers, depending on availability of techniques, tradition, training status of clinicians, and financial considerations.[142] If results suggest Alzheimer's disease, the patient might be put on a cocktail of anti-amyloid compounds, anti-tau drugs, synaptic enhancers, repurposed drugs producing small epigenetic changes, and perhaps even gene therapy directed at *APOE4*, and progression to dementia would be monitored. Imaging will be used to monitor the efficacy of the treatment in removing amyloid and tau from the brain and to tailor the treatment regimen, whereas biomarkers will be used to monitor effects on neuronal and synaptic degeneration. As a result of the developments discussed

Alzheimer's disease

Philip Scheltens, Kaj Blennow, Monique M B Breteler, Bart de Strooper, Giovanni B Frisoni, Stephen Salloway, Wiesje Maria Van der Flier

	FINGER[185]	MAPT[186]	PreDIVA[187]	HATICE[188]
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1·5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

***Table 4*: Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease**

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
Pioglitazone	PPARγ agonist that acts as a β-secretase inhibitor: inhibits first protease needed for Aβ production	TOMMORROW (NCT01931566; phase 3)	3500 people aged 65–83 years with healthy cognition at risk of developing MCI due to AD, with risk stratification including age and *TOMM40* and *APOE* genotype; a masked extension is planned with the aim of recruiting 316 participants who complete TOMMORROW with a diagnosis of MCI due to AD (NCT02284906; phase 3)	5 years (completion by 2019); extension study 2 years (completion in 2021)
Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	A4 study (NCT02008357; phase 3)	1150 people aged 65–85 years with healthy cognition, 500 of whom show evidence of brain amyloid accumulation	3 years plus 2 years' follow-up (completion by 2020)
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*)	2 years plus 3 years' follow-up (completion by 2019)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*)	2 years plus 3 years' follow-up (completion by 2019)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	API—autosomal dominant AD (NCT01998841; phase 2)	300 members of Colombian families with early-onset familial AD (age 30–60 years), including 200 carriers of an autosomal dominant AD-causing mutation in *PSEN1*	3 years plus 2 years' follow-up (completion by 2020)

Only selected phase 2 or 3 RCTs due for completion after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. PPARγ=peroxisome proliferator-activated receptor γ. Aβ=amyloid β. MCI=mild cognitive impairment. AD=Alzheimer's disease. A4 study=Anti-Amyloid Treatment in Asymptomatic Alzheimer's study. DIAN-TU=Dominantly Inherited Alzheimer Network Trial Unit. API=Alzheimer's Prevention Initiative.

Table 11: **Drugs in late-stage clinical development for Alzheimer's disease in people at risk of developing the disorder**

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for Aβ production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for Aβ production	APECS (NCT01953601; phase 3)	1500 people aged 50–85 years with prodromal AD	2 years (completion in 2018)
JNJ-54861911	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02260674 (phase 2)	100 people aged 50–85 years with early (pre-dementia) AD; an extension study of 100 people with early AD (50–85 years) who participated in previous phase 1 and phase 2 RCTs with the drug is ongoing (NCT02406027; phase 2)	10 months (completion in 2016); extension study 2 years (completion in 2024)
Reduced aggregation or oligomerisation of amyloid				
PQ912	Glutaminyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified Aβ peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01224106 (phase 3)	799 people aged 50–85 years with prodromal AD	2 years (completion in 2015)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	2700 people (1350 per trial) aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Intravenous immunoglobulin derived from healthy donors	Passive immunotherapy (contains naturally occurring polyclonal anti-Aβ antibodies)	NCT01300728 (phase 2)	50 people aged 50–84 years with MCI	2 years (completion in 2017)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥60 years with MCI or mild AD dementia	About 18 months (completion in 2016)

(Table 12 continues on next page)

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Atomoxetine	Noradrenaline reuptake inhibitor (licensed): increases brain concentrations of noradrenaline	ATX-001 (NCT01522404; phase 2)	40 people aged 50–90 years with MCI	6 months (completion in 2017)
Ladostigil (TV-3326)	Acetylcholinesterase inhibitor and MAO inhibitor: increases cholinergic neurotransmission and transmission mediated by monoamines; a derivative of rasagiline and rivastigmine, it also has antioxidant properties and can modulate APP processing and cellular signalling pathways	NCT01429623 (phase 2)	200 people aged 55–85 years with MCI	3 years (completion in 2015/2016)
DAOIB	NMDA receptor regulator: enhances NMDA-receptor-mediated glutamatergic neurotransmission	NCT02239003 (phase 2)	50 people aged 50–90 years with MCI	6 months (completion in 2016)
PXT00864*	Regulates GABAergic neurotransmission (depending on the receptor, it can have antagonistic or agonistic effects)	PLEODIAL-I (NCT02361424; phase 2)	45 people aged ≥60 years with mild AD dementia; an open-label extension study, PLEODIAL-II, is ongoing (NCT02361242; phase 2)	12 weeks (completion in 2015); extension study 24 weeks
Other mechanisms of action				
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can reduce amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
Cilostazol	PDE3 inhibitor (licensed antiplatelet drug): can reduce amyloid toxicity	COMCID (NCT02491268; phase 2)	200 people aged 55–84 years with MCI	About 2 years (completion in 2018)
BI 409306 (SUB 166499)	PDE9 inhibitor: enhances synaptic plasticity and reduces amyloid toxicity	NCT02240693 (phase 2) and NCT02337907 (phase 2)	624 people aged ≥55 years with MCI due to AD	12 weeks (completion in 2016)
Simvastatin	Cholesterol-lowering drug (licensed) with antioxidant and anti-inflammatory properties: can lower brain Aβ production and reduce Aβ-mediated neurotoxicity	SIMaMCI (NCT00842920; phase 4)	520 people aged 55–90 years with amnestic MCI	2 years (completion in 2018)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. APECS=β Amyloid Production and Effects on Cognition Study. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. MAO=monoamine oxidase. APP=amyloid precursor protein. NMDA=*N*-methyl-D-aspartate. GABA=γ-aminobutyric acid. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. PDE=phosphodiesterase. SIMaMCI=Simvastatin in Amnestic Mild Cognitive Impairment. *A combination of acamprosate and baclofen (both licensed drugs).

***Table* 12: Drugs in late-stage clinical development for Alzheimer's disease in people at symptomatic, pre-dementia stages**

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for Aβ production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for Aβ production	EPOCH (NCT01739348; phase 2/3)	1960 people aged 55–85 years with mild-to-moderate dementia due to AD	18 months (completion in 2017) with 5 year double-blind extension phase
Bryostatin-1	Macrocyclic lactone (has been investigated as an antineoplastic drug): stimulates α-secretase and reduces brain amyloid burden	NCT02431468 (phase 2)	150 people aged 55–85 years with moderate-to-severe dementia due to AD	7 months (completion in 2017)
Reduced aggregation or oligomerisation of amyloid				
Carvedilol	Non-selective β-adrenoceptor blocker (approved for congestive heart failure and hypertension): prevents formation of amyloid oligomers	NCT01354444 (phase 4)	50 people with mild dementia due to AD*	6 months (completion in 2016)
PQ912	Glutaminyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified Aβ peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)

Winblad et al 2016

Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	EXPEDITION 3 (NCT01900665; phase 3)	2100 people with mild AD dementia; an open-label extension study, EXPEDITION EXT, is underway to assess safety in 1275 people with dementia due to AD (≥55 years) who previously participated in phase 3 RCTs with solanezumab (NCT01127633; phase 3)	18 months (completion in 2018); extension study 2 years (completion in 2018)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT02051608 (phase 3)	1000 people aged 50–90 years with mild AD dementia	About 2 years (completion in 2018)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid human monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	1700 people aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01723826 (phase 2)	A long-term, open-label safety extension study in 360 people with mild-to-moderate dementia due to AD who previously participated in phase 2 RCTs of the antibody	About 2 years (completion in 2017)
Albumin and immunoglobulin associated with plasmapheresis	Passive immunotherapy	AMBAR (NCT01561053; phase 2/3)	350 people aged 55–85 years with mild-to-moderate AD dementia	14 months (completion in 2016)

Winblad et al 2016

Reduced production of P-tau or reduced fibrillation or deposition of tau				
TRx0237	Tau aggregation inhibitor: reduces abnormal tau accumulation	NCT01689246 (phase 3) and NCT01689233 (phase 3)	About 1533 people aged <90 years with mild-to-moderate AD dementia	About 18 months (completion in 2016)
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥60 years with MCI or mild AD dementia	About 18 months (completion in 2016)
Liraglutide	GLP1 receptor agonist (approved diabetes drug): improves insulin brain signalling and can prevent tau hyperphosphorylation	ELAD (NCT01843075; phase 2)	206 people aged 50–85 years with mild dementia due to AD	12 months (completion in 2017)

(Table 13 continues on next page)

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Donepezil	Acetylcholinesterase inhibitor (already approved for dementia due to AD): increases brain levels of acetylcholine	NCT01129596 (phase 4), NCT01251718 (phase 4), and NCT02162251 (phase 4)	Post-marketing surveillance studies of 1600 people with mild-to-severe AD dementia*	Up to 4 years (completion in 2015/2016)
Encenicline (MT-4666, EVP-6124)	α7 nicotinic acetylcholine receptor agonist (increases cholinergic neurotransmission)	NCT02246075 (phase 2), NCT02327182 (phase 3), NCT01969136 (phase 3), and NCT01969123 (phase 3)	1930 people aged 50–85 years with mild-to-moderate AD dementia; an extension study is planned with the aim of recruiting 1000 participants from these studies (NCT02004392; phase 3)	6–12 months (completion in 2016/2017); extension study 6 months (completion in 2017)
MK-7622	Allosteric modulator of muscarinic acetylcholine receptors (postulated): enhances response to acetylcholinesterase inhibitors, increasing cholinergic neurotransmission	NCT01852110 (phase 2)	830 people aged 55–85 years with mild-to-moderate dementia due to AD	Up to 1 year (completion in 2020)
Rasagiline	MAOB inhibitor (licensed for Parkinson's disease): increases neurotransmission mediated by monoamines	R2 (NCT02359552; phase 2)	50 people aged 50–90 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
RG1577 (RO4602522	MAOB inhibitor: increases neurotransmission mediated by monoamines	NCT01677754 (phase 2)	544 people aged 50–90 years with moderate AD dementia	1 year (completion in 2015)
Idalopirdine (Lu AE58054, SGS 518)	5-HT_6 receptor antagonist: can enhance cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission	STARSHINE (NCT01955161; phase 3), STARBEAM (NCT02006641; phase 3), and STARBRIGHT (NCT02006654; phase 3)	2490 people aged ≥50 years with mild-to-moderate AD; an extension study, STAR Extension, with 1770 people from STARSHINE AND STARBEAM is ongoing (NCT02079246; phase 3)	6 months; extension study 8 months (completion in 2015/2016)
Riluzole	Decreases glutamatergic neurotransmission by inhibiting both glutamate release and postsynaptic glutamate receptor signalling	NCT01703117 (phase 2)	48 people aged 60–85 years with mild dementia due to AD	6 months (completion in 2017)
DAOIB	NMDA receptor regulator: enhances NMDA receptor-mediated glutamatergic neurotransmission	NCT02103673 (phase 2)	90 people aged ≥50 years with AD or vascular dementia at stages from mild to moderate-severe	6 weeks (completion in 2016)
Methylphenidate	Dopamine and noradrenaline reuptake inhibitor (licensed): acts as a stimulant by promoting dopaminergic and noradrenergic neurotransmission	ADMET2 (NCT02346201; phase 3)	200 people with mild-to-moderate AD dementia and apathy	6 months (completion in 2019)

Winblad et al 2016

Other mechanisms of action				
Sagramostim	Licensed synthetic form of the haemopoietic growth factor GM-CSF: promotes amyloid removal by stimulating phagocytosis	NCT01409915 (phase 2)	40 people aged 55–85 years with mild-to-moderate AD dementia	6 months (completion in 2016)
Formoterol	Longacting β_2-adrenoceptor agonist (approved for asthma and chronic obstructive pulmonary disease): can improve synaptic plasticity and reduce amyloid burden	NCT02500784 (phase 2)	60 people aged 50–85 years with mild-to-moderate dementia due to AD	1 year (completion in 2016)
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
ATP (small molecule)	Enhances metabolism and can protect against amyloid-mediated cytotoxicity	NCT02279511 (phase 2)	20 people aged 55–85 years with moderate-to-severe AD dementia	3 months (completion in 2016)
Azeliragon (PF-04494700, TTP488; small molecule)	RAGE inhibitor: can counteract brain amyloid accumulation and modulate inflammation	NCT02080364 (phase 3)	800 people aged ≥50 years with mild AD dementia	18 months (completion in 2018)
T-817MA (small molecule)	Has neurotrophic and neuroprotective properties: can protect against amyloid-mediated and tau-mediated toxicity	NCT02079909 (phase 2)	450 people aged 55–85 years with mild-to-moderate AD dementia	About 1 year (completion in 2016)
Cerebrolysin†	Peptide mixture with neurotrophic-like properties related to regulation of cell signalling: can control amyloid metabolism and has anti-apoptotic effects mediated by expression of endogenous neurotrophic factors	NCT01822951 (phase 4)	510 people aged ≥50 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
Nilvadipine	Dihydropyridine calcium channel blocker (licensed antihypertensive): can enhance brain circulation, prevent amyloid accumulation, and increase amyloid clearance	NILVAD (NCT02017340; phase 3)	500 people aged ≥50 years with mild-to-moderate AD dementia	18 months (completion in 2017)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can counteract amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)

(Table 13 continues on next page)

Winblad et al 2016

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
AZD0530 (saracatinib)	Fyn-kinase inhibitor: attenuates amyloid-mediated and tau-mediated neuronal damage	NCT02167256 (phase 2)	152 people aged 55–85 years with mild AD dementia	1 year (completion in 2016)
Masitinib (AB1010)	Selective tyrosine-kinase inhibitor: modulates neuroinflammation by regulating mast cell activity, and promotes neuroprotection by targeting Fyn kinase	NCT01872598 (phase 3)	396 people aged ≥50 years with mild-to-moderate AD dementia	6 months (completion in 2016)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. AMBAR=Alzheimer's Management by Albumin Replacement. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. ELAD=Evaluating Liraglutide in Alzheimer's Disease. MAOB=monoamine oxidase B. 5-HT=5-hydroxytryptamine. NMDA=*N*-methyl-D-aspartate. ADMET2=Apathy in Dementia Methylphenidate Trial 2. GM-CSF=granulocyte-macrophage colony-stimulating factor. ATP=adenosine triphosphate. RAGE=receptor for advanced glycation end-products. NILVAD=Nilvadipine in Mild to Moderate Alzheimer's Disease. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. *Age not provided. †A previous meta-analysis of six RCTs suggested beneficial symptomatic effects in people with mild-to-moderate dementia due to AD.[39]

Table 13: **Drugs in late-stage clinical development for Alzheimer's disease in patients with dementia**

Winblad et al 2016

Welcome

Welcome to the website of the Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia.

John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project's principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer's disease.

Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

DIAN

Site Staff MemberName	Site Staff Role (PI, SI, Psychometrician,Cog/ClinicalRaters, SC, Back-up SC, other)	Credentials/ Background	Years of ClinicalResearch (CR) Experience	Years ofCR Experience with AD Trials	Haveyoucompleted formal GCP training?	How manyregulated (FDA, EMA, etc.)studies are youcurrentlyworking on in yourrole	Whatpercentageof your time willyou be able to dedicate to thisstudy?
Giovanni B. Frisoni	PI	MD	23	8	yes	1 Phase 1 (enrolling); 2 Phase 3 (approved)	10%
Amalia C. Bruni	co-PI	MD	32	12	yes	2 phase 3	10%
Giuliano Binetti	co-PI	MD	20	20	no		10%
Orazio Zanetti	co-PI	MD	25	20	yes	1 Phase 2 enrolling; 1Phase 3approved; 1 Phase 2 approving	10%
Alessandro Padovani	co-PI	MD					

Alzheimer’s Prevention Initiative

Lancet Neurol. 2012 Dec;11(12):1048-56.

Reiman EM, et al.: Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study.

INTERPRETATION: Young adults at genetic risk for autosomal dominant Alzheimer's disease have functional and structural MRI findings and CSF and plasma biomarker findings consistent with Aβ(1-42) overproduction. Although the extent to which the underlying brain changes are either neurodegenerative or developmental remain to be determined, this study shows the earliest known biomarker changes in cognitively normal people at genetic risk for autosomal dominant Alzheimer's disease.

Alzheimer’s Prevention Initiative

The study involves the experimental anti-amyloid antibody treatment crenezumab in approximately 300 people from an extraordinarily large extended family in Colombia, who share a rare genetic mutation that typically triggers Alzheimer's symptoms around age 45.

Ha già preso il largo negli Stati Uniti un ambizioso progetto di ricerca sulla prevenzione dell'Alzheimer, alimentato dai nuovi promettenti mezzi per identificare i soggetti a rischio e dalle misure preventive che potrebbero potenzialmente rallentare la progressione della malattia.

Il programma, chiamato **Alzheimer's Prevention Initiative** e coordinato da Eric Reiman e collaboratori

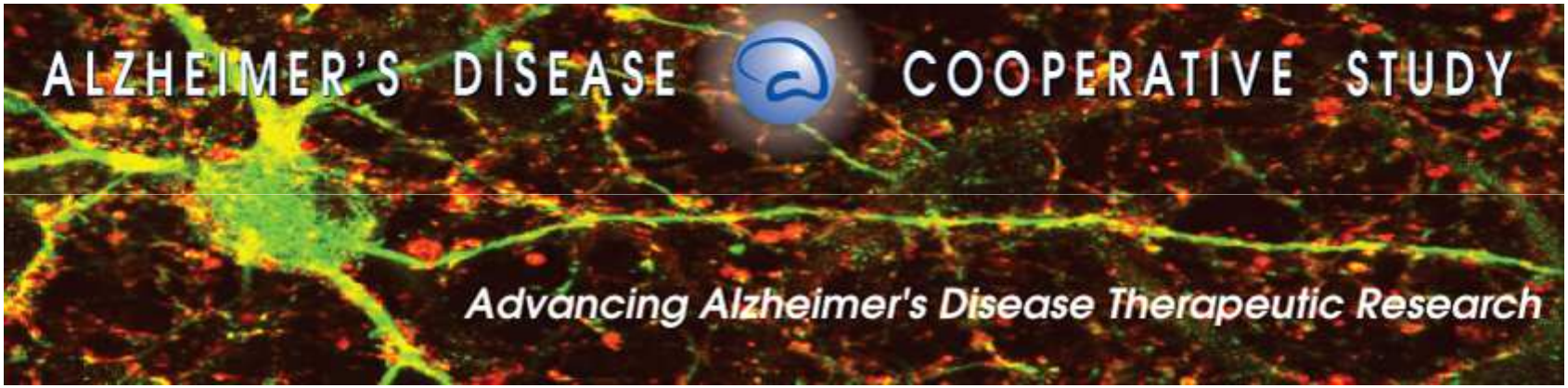
Ed è già iniziato l'arruolamento del primo dei due studi clinici del programma che coinvolgeranno ampie popolazioni di soggetti presintomatici ad altissimo rischio genetico di sviluppare una malattia di Alzheimer sintomatica. Uno studio coinvolgerà 2.000 persone residenti nell'area di Medellin, in Colombia, dove vive il gruppo di parenti più numeroso al mondo di portatori della mutazione E280A PS1, che conferisce un rischio estremamente elevato di sviluppare precocemente l'Alzheimer. I partecipanti dovranno avere un'età vicina a quella mediana di esordio clinico della malattia di Alzheimer legata a E280A PS1, che è di 47 anni.

L’altro studio,invece, riguarderà circa 50.000 cittadini nordamericani tra i 60 e gli 80 anni, di cui sarà analizzato il genotipo ApoE.

I due studi **dell’Alzheimer’s Prevention Initiative** costituiranno il primo vero test della validità dell’ipotesi della cascata amiloide nella patogenesi della demenza di Alzheimer, secondo la quale l’accumulo della proteina amiloide giocherebbe un ruolo critico nello sviluppo della malattia. Questa ipotesi, però, resta ancora da dimostrare.

Ritardare l’esordio della demenza anche solo di 5 anni senza aumentare l’aspettativa di vita vuol dire aver la possibilità di dimezzare il numero di nuovi casi, dato che l’incidenza raddoppia ogni 5 anni dopo i 60.

THE A4 TRIAL



Anti-Amyloid Treatment in Asymptomatic AD – The A4 Trial

A4 is a new secondary prevention trial effort aimed at treating older individuals at risk for developing Alzheimer's disease (AD) dementia on the basis of **having biomarker evidence of amyloid**. We will test the hypothesis that decreasing amyloid burden during the preclinical stages of AD will impact "downstream neurodegeneration" and hopefully delay cognitive decline.

To enroll in A4, clinically normal older individuals (65 and older) will be screened with PET amyloid imaging. Those found to be “amyloid-positive” - and who meet other study criteria – will be able to enroll in the trial. Subjects will be treated for three years with the anti-amyloid drug or placebo. Ideally, we will follow them beyond treatment to determine the extent of the impact on the trajectory of cognitive decline.

We anticipate that A4 will be opening to enrollment later in 2013 and we expect to have site specific information in the summer. As soon as we have additional information to share about the A4 trial, it will be posted to this website. So, please check back with us frequently.
Thank you for your interest in the A4 clinical trial.

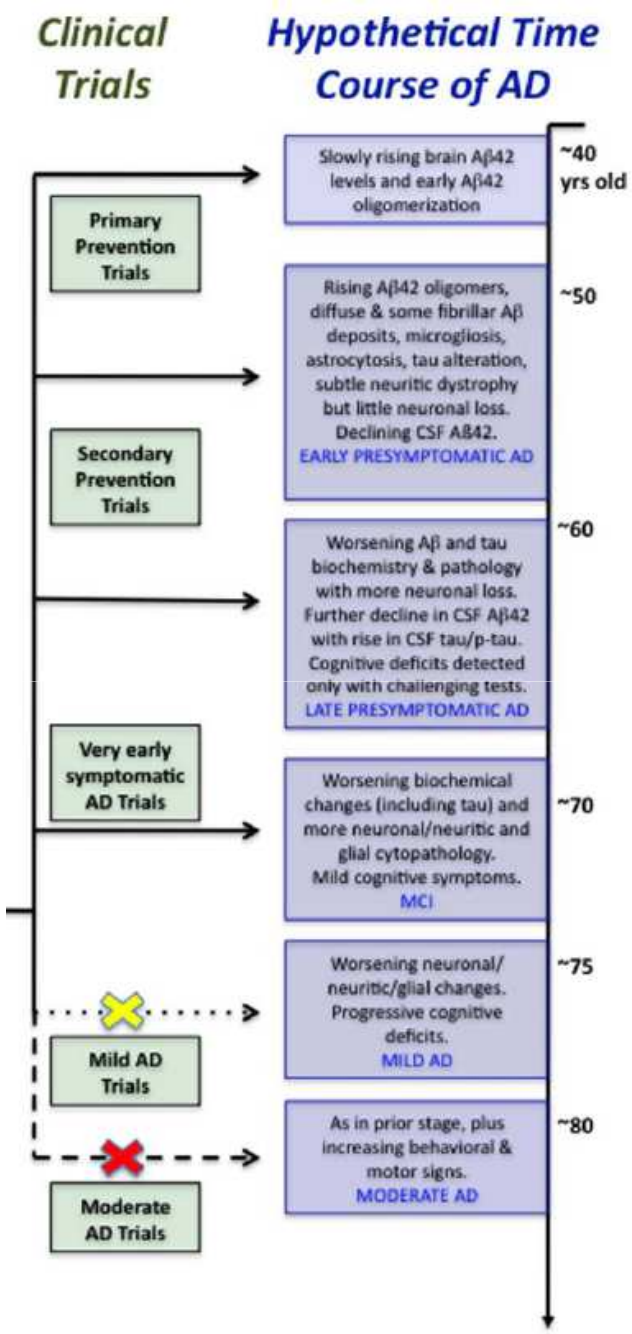
Anti-Amyloid Treatment in Asymptomatic AD – The A4 Trial

ANNALS SPECIAL EDITION: THERAPEUTIC PROSPECTS

The Therapeutics of Alzheimer's Disease: Where We Stand and Where We Are Heading

Dennis J. Selkoe, MD

ANN NEUROL 2013;74:328–336


Clinical Trials
Hypothetical Time Course of AD
Primary Prevention Trials
Secondary Prevention Trials
Very early symptomatic AD Trials
Mild AD Trials
Moderate AD Trials
Slowly rising brain Aβ42 levels and early Aβ42 oligomerization
~40 yrs old
Rising Aβ42 oligomers, diffuse & some fibrillar Aβ deposits, microgliosis, astrocytosis, tau alteration, subtle neuritic dystrophy but little neuronal loss. Declining CSF Aß42.
EARLY PRESYMPTOMATIC AD
~50
Worsening Aβ and tau biochemistry & pathology with more neuronal loss. Further decline in CSF Aβ42 with rise in CSF tau/p-tau. Cognitive deficits detected only with challenging tests.
LATE PRESYMPTOMATIC AD
~60
Worsening biochemical changes (including tau) and more neuronal/neuritic and glial cytopathology. Mild cognitive symptoms.
MCI
~70
Worsening neuronal/ neuritic/glial changes. Progressive cognitive deficits.
MILD AD
~75
As in prior stage, plus increasing behavioral & motor signs.
MODERATE AD
~80

	FINGER[185]	MAPT[186]	PreDIVA[187]	HATICE[188]
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1·5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

***Table 4*: Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease**

Winblad et al 2016

SOMMARIO

- Lo stato dell'arte
- Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)
- **Aspetti etici e conclusioni**

OPINION

Preclinical Alzheimer disease—the challenges ahead

Reisa A. Sperling, Jason Karlawish and Keith A. Johnson

Abstract | There is growing recognition that the pathophysiological process of Alzheimer disease (AD) begins many years prior to clinically obvious symptoms, and the concept of a presymptomatic or preclinical stage of AD is becoming more widely accepted. Advances in biomarker studies have enabled detection of AD pathology *in vivo* in clinically normal older individuals. The predictive value of these biomarkers at the individual patient level, however, remains to be elucidated. The ultimate goal of identifying individuals in the preclinical stages of AD is to facilitate early intervention to delay and perhaps even prevent emergence of the clinical syndrome. A number of challenges remain to be overcome before this concept can be validated and translated into clinical practice.

Sperling, R. A. *et al. Nat. Rev. Neurol.* **9**, 54–58 (2013); published online 27 November 2012; doi:10.1038/nrneurol.2012.241

- Ethical and practical concerns about disclosure of biomarker status in asymptomatic or very early symptomatic individuals need to be addressed. Solutions may vary by country. For example, in Australia, the current policy is nondisclosure of amyloid PET status, but as more is learned about the meaning of a positive amyloid scan, individuals may wish to be informed of their test results.

Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments; Eric M. Reiman, MD, JessicaB.S. Langbaum, PhD, Adam S. Fleisher, MD,Richard J. Caselli, MD, Kewei Chen, PhD, Napatkamon Ayutyanont, PhD, Yakeel T.Quiroz, MA, Kenneth S. Kosik, MD, Francisco Lopera, MD, and **Pierre N. Tariot, MD**

Lancet Neurol 2013; 12: 207–16

Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

1) **Amyloid deposition**

2) **Neurodegeneration - synaptic dysfunction**

3) **Neuronal loss – brain atrophy**

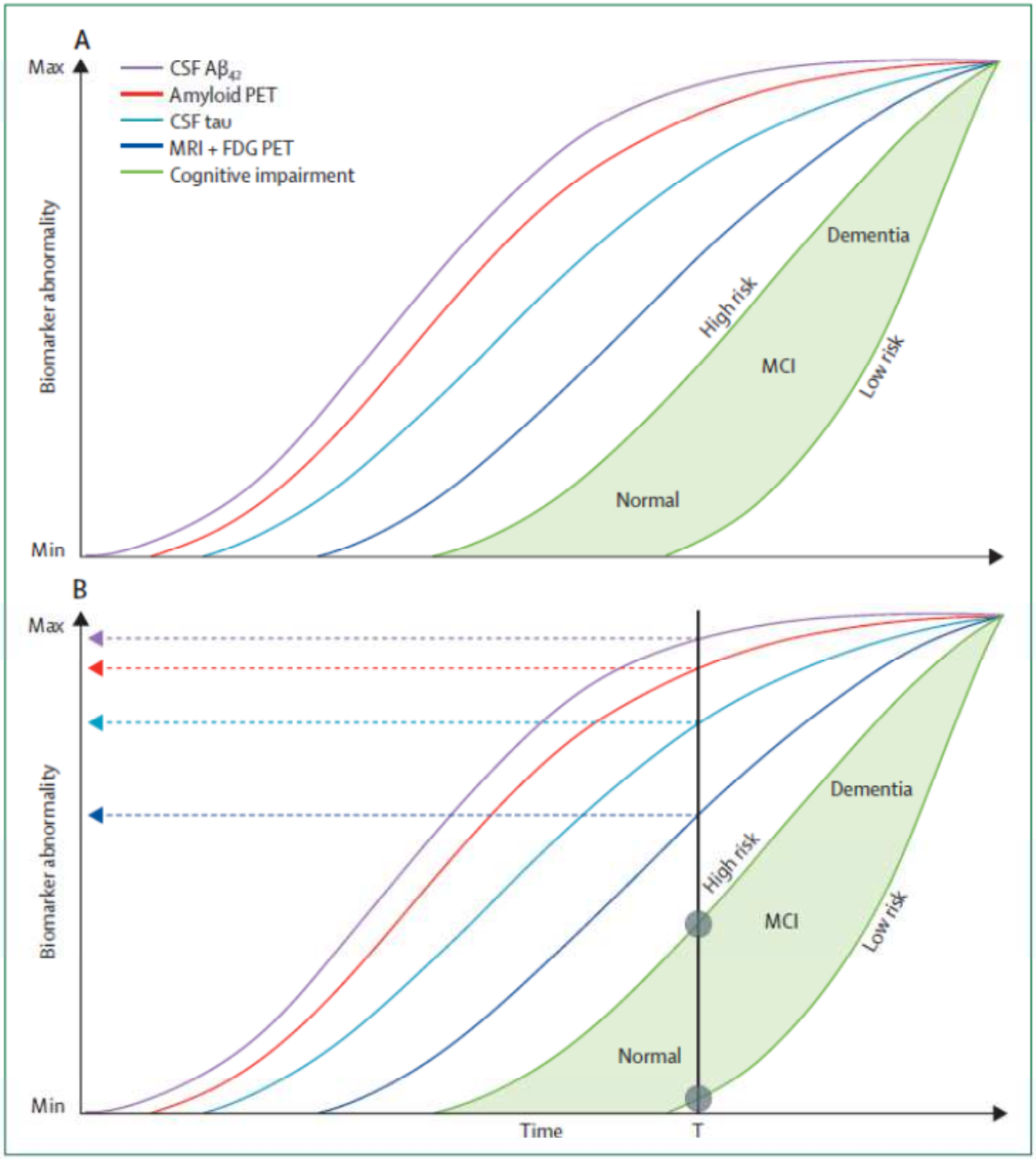


Figure 5: Revised model of dynamic biomarkers of the Alzheimer's disease pathological cascade

Lancet Neurol 2013; 12: 207–16

Lancet Neurol 2013; 12: 207–16

Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Not all patients with MCI have AD pathology and progress to dementia.

MCI negative to amyloidosis and/or neurodegeneration should not progress to dementia.

Not all patients with AD pathology progress to dementia. → **[aspetti etici]**

Uncertain progress on the fuzzy boundaries od AD

Whitehouse P.J., George D.R.

JAD, 2011;26:1-5

“The myth of Alzheimer’s”

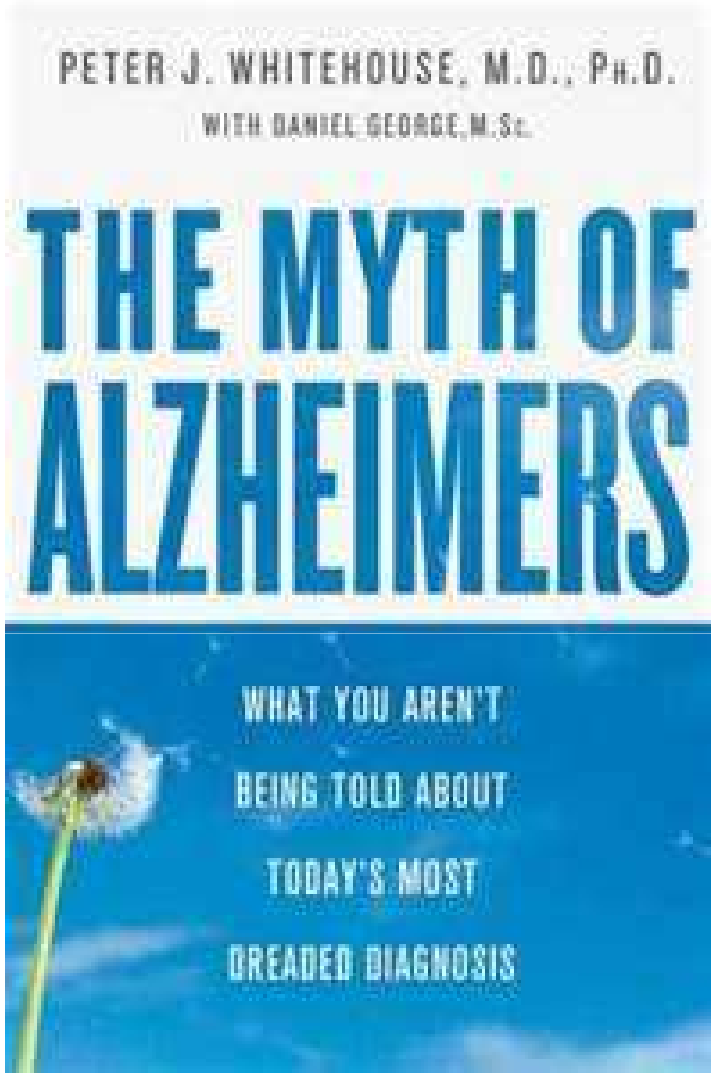
What you aren’t being told about today’s most dreaded diagnosis (2008)

Journal of Alzheimer's Disease 9 (2006) 447–453
IOS Press

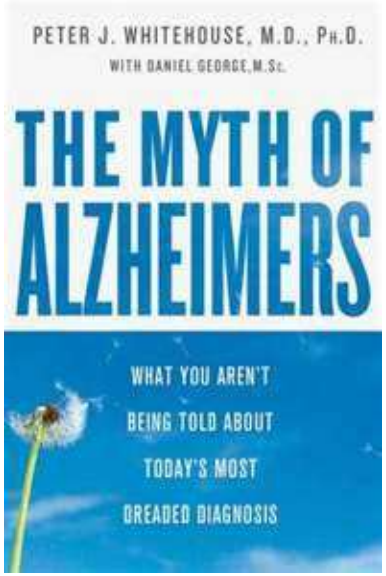
Quality of life: The bridge from the cholinergic basal forebrain to cognitive science and bioethics

Peter J. Whitehouse*
Case Western Reserve University, OH, USA

field. We are all human beings living on the same planet who age and die. We must develop a global bioethic, not a narrow superficial bioethics like the one that currently dominates medicine. This global bioethic must include a concern for social justice and sustainability of diversity of life [30].



January 2008



LA AD NON E' UNA SPECIFICA MALATTIA CEREBRALE

AD as a term for aging brain is a misnomer that militarizes our understanding of our bodies, cause us to denigrate and exclude those with the "disease".

Un approccio UMANISTICO all'invecchiamento cerebrale consentirebbe di evitare lo stigma dell'etichetta di malattia mentale.

Piuttosto che usare linguaggi "mitologici" quali "mind-wasting" , "steals the selfhood", "war against Alzheimer" dovremmo usare parole quali: **personalità, integrità, dignità per i pazienti e parole quali equilibrio, qualità della vita, responsabilità per le generazioni future, comunità, prevenzione, per riformulare le nostre priorità individuali e collettive culturali.**

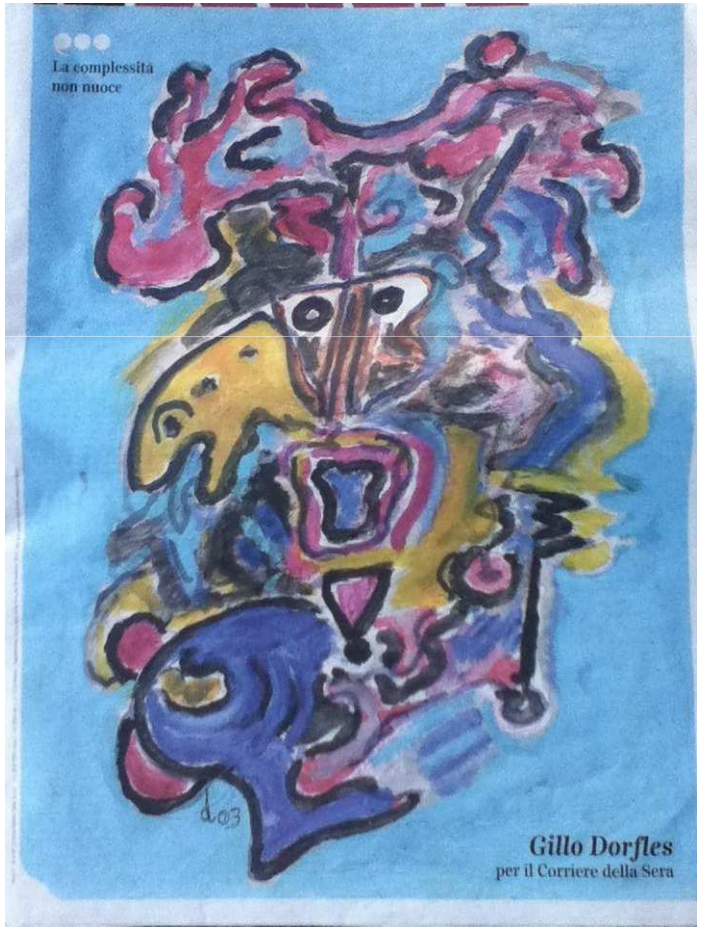
“Proprio mentre le parti superstiti del suo io diventavano sempre più piccole e frammentarie, io mi ostinavo a vederlo nella sua interezza. Continuavo ad amare, in maniera specifica e personale, l’uomo che sbadigliava in quel letto”

J. Franzen: Il Cervello di mio padre. In: Come stare soli. Einaudi, 2011.

Imparammo che a volte l'ipocrisia della verità è la cosa peggiore. … Dare ad un malato di demenza risposte secondo regole tradizionali, senza chiedersi *dove si trova* significa tentare di imporgli un mondo non suo.

La complessità non nuoce. Gillo Dorfles

Marzo 2012



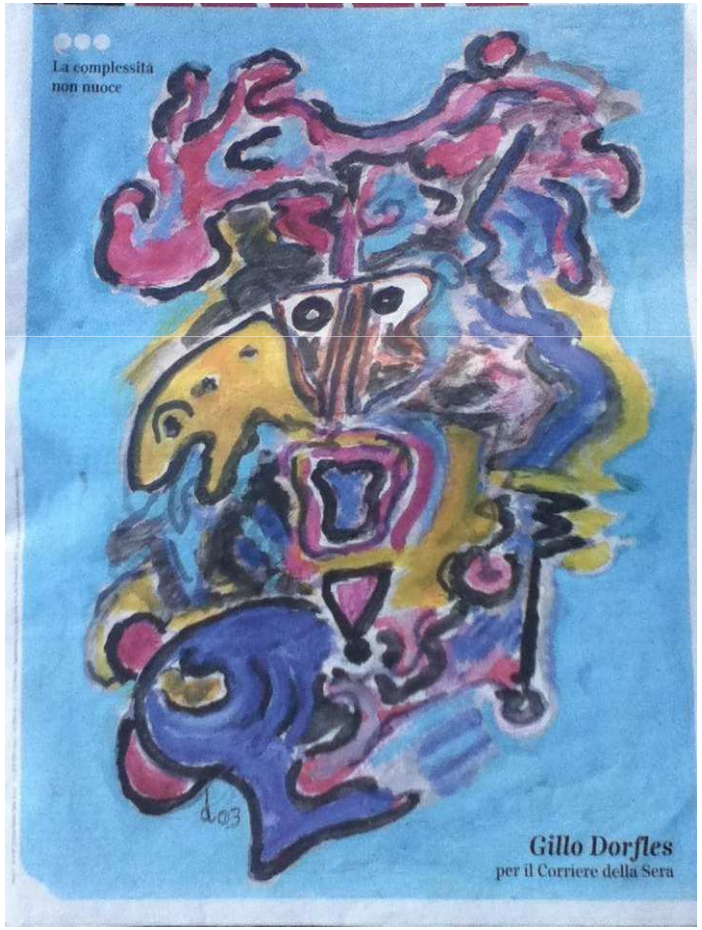
Il farmaco e …

… l’uomo che sbadigliava in quel letto.

(J. Franzen)

La complessità non nuoce. Gillo Dorfles

Marzo 2012



Il farmaco e …

… l’uomo che sbadigliava in quel letto.

(J. Franzen)