Journal Club

19 agosto 2016

Aggiornamenti in geriatria

Vi sono nuove prospettive nella ricerca di farmaci per l'Alzheimer?

Marco Trabucchi

Gruppo di ricerca geriatrica

La ricerca di un farmaco per l'Alzheimer: un esempio delle difficoltà della medicina contemporanea (biologia degli eventi di lunga durata, dimostrazione di efficacia, complessità e multiformità dei quadri clinici, probabile ricorso ad interventi plurimi).

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

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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

Gruppo di ricerca geriatrica

A Toronto (Alzheimer Conference) è stato presentato uno studio sul farmaco Lmtx, che agisce sulla proteina Tau.
Sperimentato su 891 pazienti, per 15 mesi, ha dato risultati incerti (sulla funzione?)

Lmtx: alcune parole chiave

- **Attenzione:** il campo si sta muovendo finalmente dopo anni di fallimenti e frustrazioni. Questo nuovo farmaco che agisce sulla proteina Tau sposta l'interesse verso ambiti diversi da quelli più "classici" volti a ridurre la concentrazione cerebrale di beta-amiloide. Ben venga quindi; ne seguiamo con interesse l'evoluzione!
- **Prudenza:** i dati pubblicati a Toronto sono molto incerti e non sono stati filtrati attraverso la pubblicazione su una rivista scientifica.
- **Preoccupazione** perché si può suscitare nelle famiglie degli ammalati una serie di speranze senza fondamento. Questo farmaco non potrà curare le persone già ammalate, perché quando -e se- sarà immesso in terapia potrà servire solo a pazienti nelle fasi precoci della malattia.
- **Progettazione di interventi** attenti all'evoluzione dello scenario delle terapie. Se, come ci auguriamo, all'inizio del prossimo anno verranno pubblicati dati positivi su alcuni nuovi farmaci si scatenerà una forte pressione perché vengano resi disponibili per tutti, nonostante i costi elevati. L'esperienza recente dei farmaci per l'epatite C, con le relative polemiche e incertezze, indica l'esigenza di una forte alleanza tra medici e programmatori per delineare il profilo dei pazienti che maggiormente si giovano delle nuove molecole, in modo da creare condizioni di appropriatezza, che permettano di evitare costi inutili (nonchè fallimenti terapeutici che possono danneggiare il farmaco stesso e la sua credibilità). Si apre anche un problema di quali potrebbero essere nel prossimo futuro i centri clinici a livello delle varie regioni in grado di prescrivere i nuovi farmaci in modo appropriato. Infine, vi sarà uno stanziamento ad hoc nella prossima legge di stabilità per i farmaci antidemenza?

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

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www.thelancet.com

Published online March 12, 2015

Summary

Background Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.

Methods In a double-blind randomised controlled trial we enrolled individuals aged 60–77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) *Z* score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.

Findings Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total *Z* score at 2 years was 0·20 (SE 0·02, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. Between-group difference in the change of NTB total score per year was 0·022 (95% CI 0·002–0·042, p=0·030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention *vs* no individuals for control).

Interpretation Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

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An effective treatment for AD is perhaps the greatest unmet need facing modern medicine. An organised and concerted effort among governmental agencies, academic researchers, and industry will be needed to develop effective and affordable therapies. The overall success rate of drug development for AD has been poor. A few drugs are approved for the symptomatic treatment of dementia, and several drug candidates are in clinical trials, but novel paradigms are needed to incorporate advances in early diagnosis, genetic factors, and epidemiology into the design of clinical trials for new drug candidates. Major long-term financial commitment to clinical development will be essential.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

Gruppo di ricerca geriatrica

Dieci anni (almeno) di impegno, di grandi investimenti, di speranze, di fallimenti.
Siamo alla fine della storia?
L'obiettivo 2025 è raggiungibile, come ipotizzato?

Gruppo di ricerca geriatrica

ASSOCIAZIONE ITALIANA PSICOGERIATRIA

PSICOGERIATRIA 2015; 2: 5-7

EDITORIALE

La demenza: incertezze, paure, errori

MARCO TRABUCCHI
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Gruppo di ricerca geriatrica

EDITORIAL

Caring with evidence based medicine

Evidence alone should never dictate care for a patient

The real challenge is to deal with illness and how it fragments, disarticulates, and renders uncertain the conduct and dignity of human lives.

(Hargraves I. et al, BMJ 354(8064): 10, 2016)

La diffusione di approcci generici, non controllati, al confine con l'imbroglio.
La pressione del bisogno induce comportamenti inadeguati (talvolta anche da parte di aziende importanti).

Gruppo di ricerca geriatrica

Ogni labirinto ha un'uscita, ma i tentativi di trovarla passano attraverso errori e false speranze, le scelte ai bivi non sono sempre basate su un calcolo razionale. È possibile accettare un tale atteggiamento nella ricerca? L'approccio razionale, il proporre ipotesi di lavoro e verificarle, è irrinunciabile, ma allo stesso tempo, accettando la logica del labirinto, bisogna essere sempre pronti a tornare indietro e ripartire con l'esplorazione.

(Govoni S., 2015)

Gruppo di ricerca geriatrica

Alcune indicazioni per uno sviluppo razionale delle ricerche.

(1) Improvements in the clinical-development infrastructure are needed, with increased collaboration between governments, public and private institutions, AD associations, and the pharmaceutical industry to facilitate clinical research. Substantial redundant research in AD drug development should be avoided.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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(2) Increased research budgets are needed for drug discovery, drug development, and clinical trials. International cohorts, standardised methods, and ethical and regulatory frameworks should be established to facilitate clinical studies. Clinical drug development and clinical trials should be coordinated internationally. New approaches to drug development (eg, for different treatment aims) should be recognised and supported.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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(3) Public, private, and corporate funding decisions should be based on evidence and scientific merit, rather than being driven by advocacy, opinion, persuasion, or corporate considerations.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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(4) The voice of patients should be strengthened in risk-based approaches to the conduct of early first-in-human clinical trials in which the preclinical evidence base is weak. Options should be discussed for earlier entry of patients into clinical-development programmes, enabling the collection of valuable pharmacokinetic and pharmacodynamic information from participants. This approach would help to refine adaptive clinical trials and enable early failure.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

(5) More patients should be invited to participate in research. Registries of elderly patients with and without cognitive impairment are needed to facilitate recruitment into trials.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

(6) A more synchronised approach is needed for the implementation of regulatory processes for the conduct of clinical trials in national laws.[412,413]

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

Targets for future drugs:

- Beta-amyloid
- Beta-secretase
- Tau protein
- Inflammation
- Insulin resistance
- Oxidation
- Al
- Copper

La possibilità di politrattamenti, per diversi target della stessa malattia.

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I tre approcci clinici

- **persone a rischio**
- **persone sintomatiche, ma non dementi**
- **persone affette da demenza**

Gruppo di ricerca geriatrica

Mancano ancora dati sulla sequenza: alterazione biologica (genetica o ambientale), primi segni a livello preclinico, diagnosi nelle fasi iniziali, sintomi nelle fasi avanzate.
Cosa accade nei lunghi anni di storia naturale?

Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia

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ABSTRACT

Objective: To examine the relation of performance on brief cognitive tests to development of clinically diagnosed Alzheimer disease (AD) dementia over the following 18 years in a sample of African Americans and European Americans.

Methods: A composite cognitive test score based on tests of episodic memory, executive function, and global cognition was constructed in a prospective population-based sample of 2,125 participants (55% African American and 61% female) aged 65 years and older residing in 4 Chicago neighborhoods. Time before AD dementia diagnosis was categorized into 6 groups corresponding to data collection periods: 0.1–0.9, 1.0–3.9, 4.0–6.9, 7.0–9.9, 10.0–12.9, and 13.0–17.9 years.

Results: Of 2,125 participants without clinical AD dementia, 442 (21%) developed clinical AD dementia over 18 years of follow-up. Lower composite cognitive test scores were associated with the development of AD dementia over the duration of the study. The magnitude of association between composite cognitive test score and development of AD dementia increased from an odds ratio of 3.39 (95% confidence interval 1.72, 6.67; $p < 0.001$) at 13.0–17.9 years to 9.84 (95% confidence interval 7.41, 13.06; $p < 0.001$) at 0.1–0.9 years, per SD increment. These associations were consistently larger among European Americans than among African Americans. Performance on individual cognitive tests of episodic memory, executive function, and global cognition also significantly predicted the development of AD dementia, with associations exhibiting a similar trend over 18 years.

Conclusions: Our findings suggest that cognitive impairment may manifest in the preclinical phase of AD dementia substantially earlier than previously established. *Neurology®* 2015;85:1–7

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Table 2 Time to diagnosis of clinical AD dementia and number of participants who developed AD dementia during an 18-year period after initial cognitive testing

	African Americans			European Americans		
Years before AD dementia diagnosis	No.	Time to diagnosis[a]	AD dementia, n (%)	No.	Time to diagnosis[a]	AD dementia, n (%)
0.1–0.9	864	0.5 (0.22)	186 (22)	673	0.5 (0.22)	114 (17)
1.0–3.9	948	2.8 (0.98)	242 (26)	838	2.8 (0.98)	148 (18)
4.0–6.9	901	5.4 (1.04)	214 (24)	745	5.5 (1.01)	121 (16)
7.0–9.9	665	8.4 (1.05)	151 (23)	432	8.6 (1.05)	67 (16)
10.0–12.9	281	11.3 (1.05)	72 (26)	225	11.3 (1.13)	35 (16)
13.0–17.9	265	14.7 (1.45)	61 (23)	164	14.4 (1.31)	17 (10)

Abbreviation: AD = Alzheimer disease.
[a] Mean (SD) time in years between cognitive test scores and clinical evaluation for diagnosis of AD dementia.

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Neurology® 2015;85:1–7

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

	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.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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

	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., Lancet Neurol. 15: 455-532, 2016)

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

	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).

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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

	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)

(Table 13 continues on next page)

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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

	Mechanism	RCTs	Participants	Duration
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)
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., Lancet Neurol. 15: 455-532, 2016)

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

	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)

(Table 13 continues on next page)

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

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

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
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., Lancet Neurol. 15: 455-532, 2016)

Gruppo di ricerca geriatrica

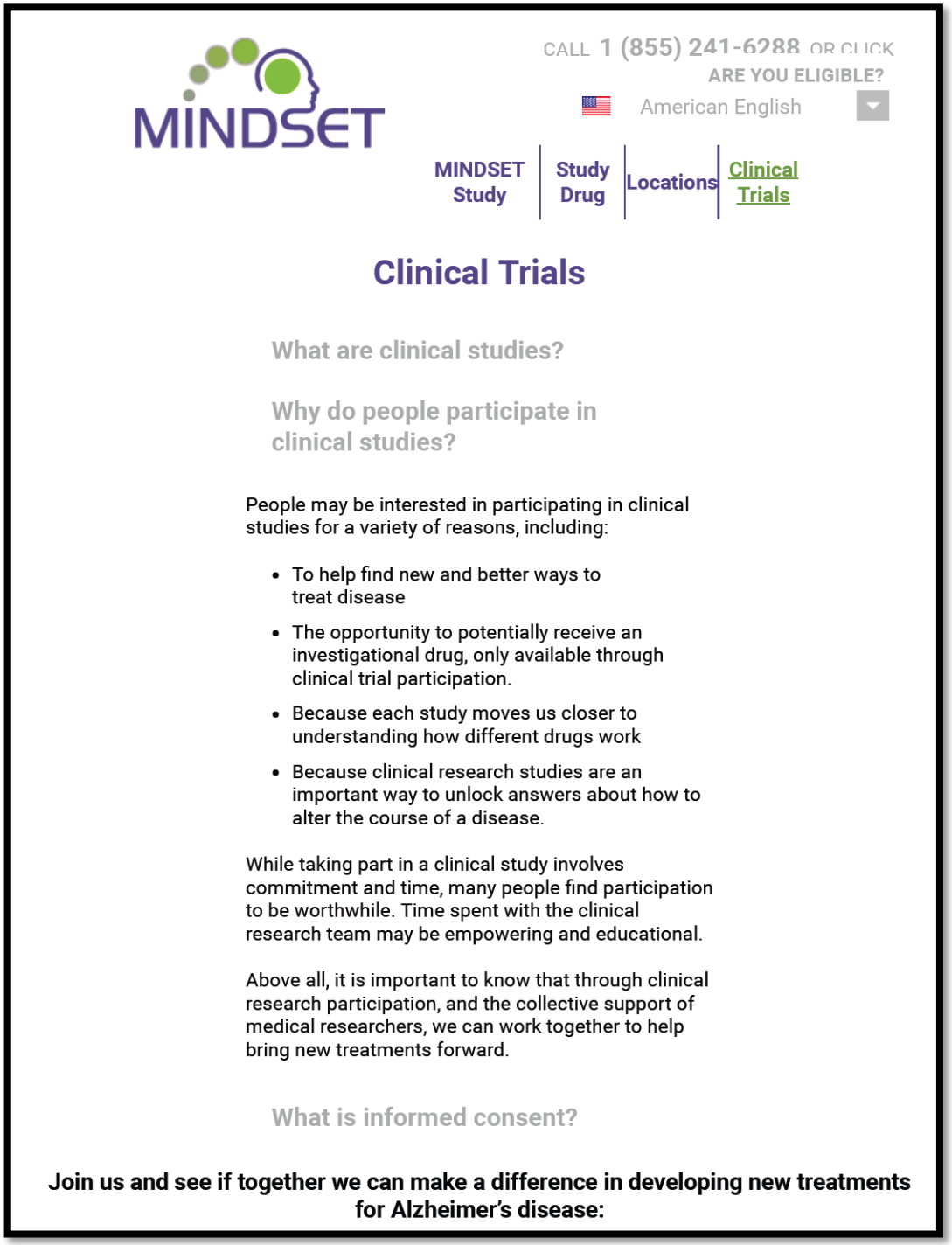
Table 13: Drugs in late-stage clinical development for Alzheimer's disease in patients with dementia

	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.[390]

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

La partecipazione della famiglia



Gruppo di ricerca geriatrica

http://www.alzheimersglobalstudy.com/en-us/trials

Alzheimer's Reading Room

"The best way to find answers and solutions to the problems that Alzheimer's care and dementia professionals face each day."

10 Commandments of Alzheimer's Caregiving

Words of wisdom from our expert and memory care and caregiver expert Dr. Rita Jablonski-Jaudon.

Learn More and Share

Investigation Drug Intepirdine (RVT-101) is now being investigated in a Phase 3 clinical trial and is accepting Alzheimer's patients with MMSE scores as low as 12 (moderate to severe)

Gruppo di ricerca geriatrica

L’esempio della idalopirdine

Safety and efficacy of idalopirdine, a 5-HT_6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial

David Wilkinson, Kristian Windfeld, Eskild Colding-Jørgensen

Lancet Neurol 2014; 13: 1092–99

Summary

Background In human beings, 5-HT_6 receptors are almost exclusively expressed in the brain, particularly in areas relevant for cognition, such as the hippocampus and frontal cortex. We assessed the effect on cognitive performance of Lu AE58054 (idalopirdine), a selective 5-HT_6 receptor antagonist, in donepezil-treated patients with moderate Alzheimer's disease.

Methods For this randomised, double-blind, placebo-controlled phase 2 trial (LADDER), we recruited patients from 48 outpatient clinical sites in seven countries. Patients were 50 years or older, had moderate Alzheimer's disease (a mini-mental state examination score of 12–19), and had been stably treated with donepezil 10 mg per day for 3 or more months. Using a computer-generated sequence, we randomly assigned patients (1:1, stratified by site) to receive either idalopirdine 90 mg per day (30 mg thrice daily) or placebo. The primary endpoint was change from baseline in the 11-item Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) at week 24. We analysed all efficacy endpoints in the full-analysis set (modified intention-to-treat analysis). This trial is registered with ClinicalTrials.gov, number NCT01019421.

Findings Between Dec 8, 2009, and Dec 23, 2011, we randomly allocated 278 patients to treatment: 133 to placebo and 145 to idalopirdine. 132 patients in the placebo group and 140 in the experimental group were included in the final analysis. At week 24, the change from baseline in ADAS-cog total score was +1·38 (SD 0·53) in the placebo group and –0·77 (0·55) in the idalopirdine group (treatment difference of –2·16 points, 95% CI –3·62 to –0·69; p=0·0040). 25 patients (seven taking placebo and 18 taking idalopirdine) discontinued treatment because of adverse events, the difference between groups being mainly due to asymptomatic transient increases in transaminase concentrations in some idalopirdine-treated patients. The most common adverse events (occurring in >3% of patients) were increased γ-glutamyltransferase (14 [10%] patients in the idalopirdine group *vs* two [2%] in the placebo group), diarrhoea (six [4%] *vs* nine [7%]), urinary tract infection (three [2%] *vs* nine [7%]), fall (three [2%] *vs* eight [6%]), increased alanine aminotransferase (nine [6%] *vs* none), and benign prostatic hyperplasia (two [5%] *vs* none). Serious adverse events were reported by 14 (10%) patients in the idalopirdine group and 13 (10%) patients in the placebo group. One death occurred in each treatment group, neither were regarded as being related to treatment.

Interpretation Idalopirdine improved cognitive function in donepezil-treated patients with moderate Alzheimer's disease. Larger studies in a broader population of patients are ongoing to substantiate the effects reported here.

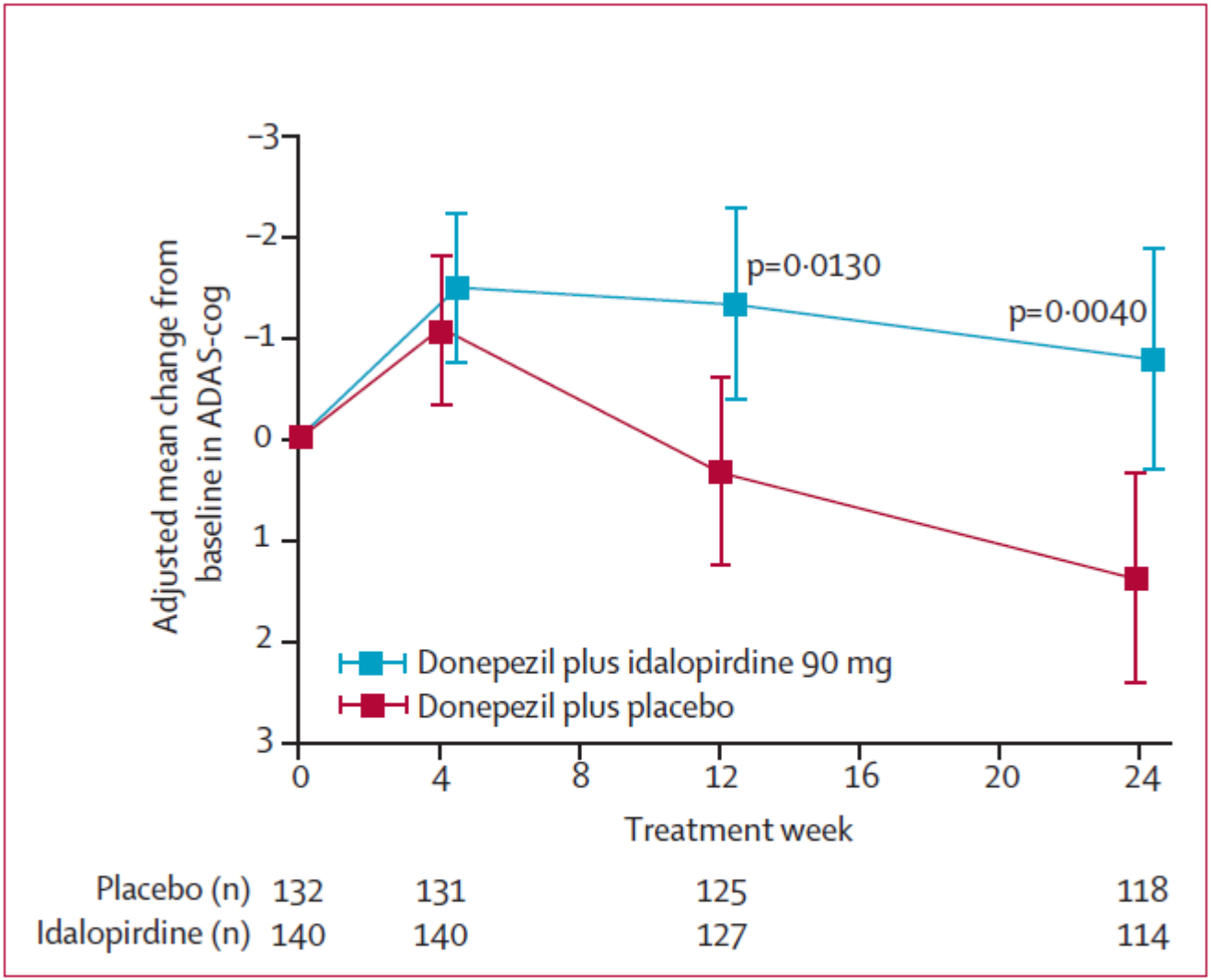


Figure 2: **Adjusted mean change in ADAS-cog (full-analysis set, MMRM by visit)**
Error bars are 95% CI. ADAS-cog=11-item Alzheimer's Disease Assessment Scale, Cognitive Subscale. MMRM=mixed model, repeated measures.

David Wilkinson, Kristian Windfeld, Eskild Colding-Jørgensen ***Lancet Neurol*** **2014; 13: 1092–99**

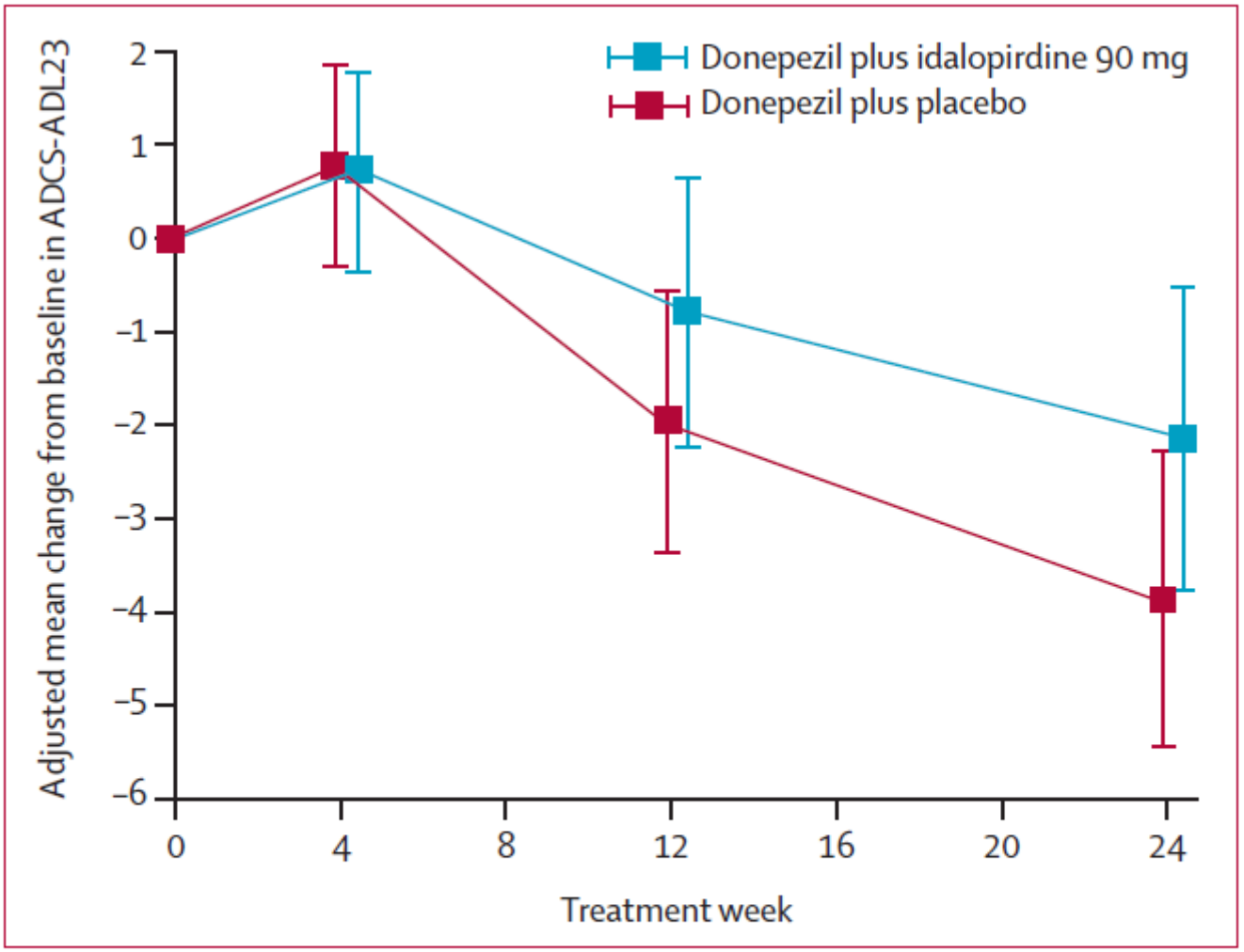


***Figure* 3: Adjusted mean change in ADCS-ADL23 (full-analysis set, MMRM by visit)**

Error bars are 95% CI. ADCS-ADL23=23-item Alzheimer's Disease Cooperative Study Activities of Daily Living scale. MMRM=mixed model, repeated measures.

David Wilkinson, Kristian Windfeld, Eskild Colding-Jørgensen ***Lancet Neurol* 2014; 13: 1092–99**

Gruppo di ricerca geriatrica

Alcuni ulteriori esempi
(che dimostrano l'incertezza dello scenario)

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A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease

OPEN

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ABSTRACT

Objective: A randomized, placebo-controlled, double-blind, multicenter 52-week phase 2 trial of resveratrol in individuals with mild to moderate Alzheimer disease (AD) examined its safety and tolerability and effects on biomarker (plasma Aβ40 and Aβ42, CSF Aβ40, Aβ42, tau, and phospho-tau 181) and volumetric MRI outcomes (primary outcomes) and clinical outcomes (secondary outcomes).

Methods: Participants (n = 119) were randomized to placebo or resveratrol 500 mg orally once daily (with dose escalation by 500-mg increments every 13 weeks, ending with 1,000 mg twice daily). Brain MRI and CSF collection were performed at baseline and after completion of treatment. Detailed pharmacokinetics were performed on a subset (n = 15) at baseline and weeks 13, 26, 39, and 52.

Results: Resveratrol and its major metabolites were measurable in plasma and CSF. The most common adverse events were nausea, diarrhea, and weight loss. CSF Aβ40 and plasma Aβ40 levels declined more in the placebo group than the resveratrol-treated group, resulting in a significant difference at week 52. Brain volume loss was increased by resveratrol treatment compared to placebo.

Conclusions: Resveratrol was safe and well-tolerated. Resveratrol and its major metabolites penetrated the blood–brain barrier to have CNS effects. Further studies are required to interpret the biomarker changes associated with resveratrol treatment.

Classification of evidence: This study provides Class II evidence that for patients with AD resveratrol is safe, well-tolerated, and alters some AD biomarker trajectories. The study is rated Class II because more than 2 primary outcomes were designated. *Neurology*® 2015;85:1–9

Targeting Prodromal Alzheimer Disease With Avagacestat

A Randomized Clinical Trial

Vladimir Coric, MD[1]; Stephen Salloway, MD[2]; Christopher H. van Dyck, MD[3]; Bruno Dubois, MD[4]; Niels Andreasen, MD, PhD[5]; Mark Brody, MD[6]; Craig Curtis, MD[7]; Hilkka Soininen, MD[8]; Stephen Thein, PhD[9]; Thomas Shiovitz, MD[10]; Gary Pilcher, PhD[1]; Steven Ferris, PhD[11]; Susan Colby, BA[1]; Wendy Kerselaers, BA[1]; Randy Dockens, PhD[1]; Holly Soares, PhD[1]; Stephen Kaplita, MSc[1]; Feng Luo, PhD[1]; Chahin Pachai, PhD[12]; Luc Bracoud, MSc[12]; Mark Mintun, MD[13]; Joshua D. Grill, PhD[14]; Ken Marek, MD[15]; John Seibyl, MD[15]; Jesse M. Cedarbaum, MD[1]; Charles Albright, PhD[1]; Howard H. Feldman, MD[16]; Robert M. Berman, MD[1]

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JAMA Neurol. 2015;72(11):1324-1333. doi:10.1001/jamaneurol.2015.0607.

Importance Early identification of Alzheimer disease (AD) is important for clinical management and affords the opportunity to assess potential disease-modifying agents in clinical trials. To our knowledge, this is the first report of a randomized trial to prospectively enrich a study population with prodromal AD (PDAD) defined by cerebrospinal fluid (CSF) biomarker criteria and mild cognitive impairment (MCI) symptoms.

Objectives To assess the safety of the γ-secretase inhibitor avagacestat in PDAD and to determine whether CSF biomarkers can identify this patient population prior to clinical diagnosis of dementia.

Design, Setting, and Participants A randomized, placebo-controlled phase 2 clinical trial with a parallel, untreated, nonrandomized observational cohort of CSF biomarker-negative participants was conducted May 26, 2009, to July 9, 2013, in a multicenter global population. Of 1358 outpatients screened, 263 met MCI and CSF biomarker criteria for randomization into the treatment phase. One hundred two observational cohort participants who met MCI criteria but were CSF biomarker-negative were observed during the same study period to evaluate biomarker assay sensitivity.

Interventions Oral avagacestat or placebo daily.

Main Outcomes and Measure Safety and tolerability of avagacestat.

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Targeting Prodromal Alzheimer Disease With Avagacestat

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[+] Author Affiliations

JAMA Neurol. 2015;72(11):1324-1333. doi:10.1001/jamaneurol.2015.0607.

Results Of the 263 participants in the treatment phase, 132 were randomized to avagacestat and 131 to placebo; an additional 102 participants were observed in an untreated observational cohort. Avagacestat was relatively well tolerated with low discontinuation rates (19.6%) at a dose of 50 mg/d, whereas the dose of 125 mg/d had higher discontinuation rates (43%), primarily attributable to gastrointestinal tract adverse events. Increases in nonmelanoma skin cancer and nonprogressive, reversible renal tubule effects were observed with avagacestat. Serious adverse event rates were higher with avagacestat (49 participants [37.1%]) vs placebo (31 [23.7%]), attributable to the higher incidence of nonmelanoma skin cancer. At 2 years, progression to dementia was more frequent in the PDAD cohort (30.7%) vs the observational cohort (6.5%). Brain atrophy rate in PDAD participants was approximately double that of the observational cohort. Concordance between abnormal amyloid burden on positron emission tomography and pathologic CSF was approximately 87% ($\kappa = 0.68$; 95% CI, 0.48-0.87). No significant treatment differences were observed in the avagacestat vs placebo arm in key clinical outcome measures.

Conclusions and Relevance Avagacestat did not demonstrate efficacy and was associated with adverse dose-limiting effects. This PDAD population receiving avagacestat or placebo had higher rates of clinical progression to dementia and greater brain atrophy compared with CSF biomarker–negative participants. The CSF biomarkers and amyloid positron emission tomography imaging were correlated, suggesting that either modality could be used to confirm the presence of cerebral amyloidopathy and identify PDAD.

Original Investigation

Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function
The AREDS2 Randomized Clinical Trial

Emily Y. Chew, MD; Traci E. Clemons, PhD; Elvira Agrón, MA; Lenore J. Launer, PhD; Francine Grodstein, ScD; Paul S. Bernstein, MD, PhD; for the Age-Related Eye Disease Study 2 (AREDS2) Research Group

IMPORTANCE Observational data have suggested that high dietary intake of saturated fat and low intake of vegetables may be associated with increased risk of Alzheimer disease.

OBJECTIVE To test the effects of oral supplementation with nutrients on cognitive function.

DESIGN, SETTING, AND PARTICIPANTS In a double-masked randomized clinical trial (the Age-Related Eye Disease Study 2 [AREDS2]), retinal specialists in 82 US academic and community medical centers enrolled and observed participants who were at risk for developing late age-related macular degeneration (AMD) from October 2006 to December 2012. In addition to annual eye examinations, several validated cognitive function tests were administered via telephone by trained personnel at baseline and every 2 years during the 5-year study.

INTERVENTIONS Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo were tested in a factorial design. All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc.

(continued...)

JAMA. 2015;314(8):791-801. doi:10.1001/jama.2015.9677

Original Investigation

Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function
The AREDS2 Randomized Clinical Trial

Emily Y. Chew, MD; Traci E. Clemons, PhD; Elvira Agrón, MA; Lenore J. Launer, PhD; Francine Grodstein, ScD; Paul S. Bernstein, MD, PhD; for the Age-Related Eye Disease Study 2 (AREDS2) Research Group

JAMA. 2015;314(8):791-801. doi:10.1001/jama.2015.9677

MAIN OUTCOMES AND MEASURES The main outcome was the yearly change in composite scores determined from a battery of cognitive function tests from baseline. The analyses, which were adjusted for baseline age, sex, race, history of hypertension, education, cognitive score, and depression score, evaluated the differences in the composite score between the treated vs untreated groups. The composite score provided an overall score for the battery, ranging from −22 to 17, with higher scores representing better function.

RESULTS A total of 89% (3741/4203) of AREDS2 participants consented to the ancillary cognitive function study and 93.6% (3501/3741) underwent cognitive function testing. The mean (SD) age of the participants was 72.7 (7.7) years and 57.5% were women. There were no statistically significant differences in change of scores for participants randomized to receive supplements vs those who were not. The yearly change in the composite cognitive function score was −0.19 (99% CI, −0.25 to −0.13) for participants randomized to receive LCPUFAs vs −0.18 (99% CI, −0.24 to −0.12) for those randomized to no LCPUFAs (difference in yearly change, −0.03 [99% CI, −0.20 to 0.13]; P = .63). Similarly, the yearly change in the composite cognitive function score was −0.18 (99% CI, −0.24 to −0.11) for participants randomized to receive lutein/zeaxanthin vs −0.19 (99% CI, −0.25 to −0.13) for those randomized to not receive lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, −0.14 to 0.19]; P = .66). Analyses were also conducted to assess for potential interactions between LCPUFAs and lutein/zeaxanthin and none were found to be significant.

CONCLUSIONS AND RELEVANCE Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.

Radiology

Multimodal Randomized Functional MR Imaging of the Effects of Methylene Blue in the Human Brain[1]

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Jinqi Li, MD
Jack L. Lancaster, PhD
Francisco Gonzalez-Lima, PhD
Timothy Q. Duong, PhD

Purpose: To investigate the sustained-attention and memory-enhancing neural correlates of the oral administration of methylene blue in the healthy human brain.

Materials and Methods: The institutional review board approved this prospective, HIPAA-compliant, randomized, double-blinded, placebo-controlled clinical trial, and all patients provided informed consent. Twenty-six subjects (age range, 22–62 years) were enrolled. Functional magnetic resonance (MR) imaging was performed with a psychomotor vigilance task (sustained attention) and delayed match-to-sample tasks (short-term memory) before and 1 hour after administration of low-dose methylene blue or a placebo. Cerebrovascular reactivity effects were also measured with the carbon dioxide challenge, in which a 2 × 2 repeated-measures analysis of variance was performed with a drug (methylene blue vs placebo) and time (before vs after administration of the drug) as factors to assess drug × time between group interactions. Multiple comparison correction was applied, with cluster-corrected $P < .05$ indicating a significant difference.

Results: Administration of methylene blue increased response in the bilateral insular cortex during a psychomotor vigilance task ($Z = 2.9–3.4$, $P = .01–.008$) and functional MR imaging response during a short-term memory task involving the prefrontal, parietal, and occipital cortex ($Z = 2.9–4.2$, $P = .03–.0003$). Methylene blue was also associated with a 7% increase in correct responses during memory retrieval ($P = .01$).

Conclusion: Low-dose methylene blue can increase functional MR imaging activity during sustained attention and short-term memory tasks and enhance memory retrieval.

Gruppo di ricerca geriatrica

Cannabinoids remove plaque-forming Alzheimer's proteins from brain cells

Preliminary lab studies at the Salk Institute find THC reduces beta amyloid proteins in human neurons

Salk Institute scientists have found preliminary evidence that tetrahydrocannabinol (THC) and other compounds found in marijuana can promote the cellular removal of amyloid beta, a toxic protein associated with Alzheimer's disease.

While these exploratory studies were conducted in neurons grown in the laboratory, they may offer insight into the role of inflammation in Alzheimer's disease and could provide clues to developing novel therapeutics for the disorder.

Although other studies have offered evidence that cannabinoids might be neuroprotective against the symptoms of Alzheimer's, we believe our study is the first to demonstrate that cannabinoids affect both inflammation and amyloid beta accumulation in nerve cells.

(Currais A. et al, Aging Mechanisms Disease 2016 (2):1-8)

The use of effective strategies to prevent or cure AD and other dementias will demand an urgent reassessment of traditional paradigms of health-care practice.

Although basic biomedical research initiated by individual investigators can lead to breakthroughs and important discoveries, and the pharmaceutical industry has had an unparalleled series of successes over many decades, a disease threat as large and complex as AD in an ageing population cannot be left to the fortunes of unfocused research programmes on the one hand, or to the whims of corporate risk–return business analysis on the other.

A public–private partnership on a multinational scale is needed, and the EU is well positioned—in view of its excellent health-care delivery system, basic single payer model, outstanding research infrastructure, and strong pharmaceutical industry base—to take the world lead, in partnership with international organisations, to develop new approaches to prevent or cure AD and other dementias and to provide models of compassionate care for patients with dementia.

(Winblad et al., Lancet Neurol. 15: 455-532, 2016)

Gruppo di ricerca geriatrica

Le speranze del 2017 …
fino al 2025