68° CONGRESSO NAZIONALE SIGG
SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
Ritorno al futuro
FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

MCI e Demenza Vascolare : i donatori di colina non sono tutti uguali

ASL CITTÀ DI TORINO

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Responsabile Area RSA e Strutture Residenziali DIRMEI - Reg. Piemonte

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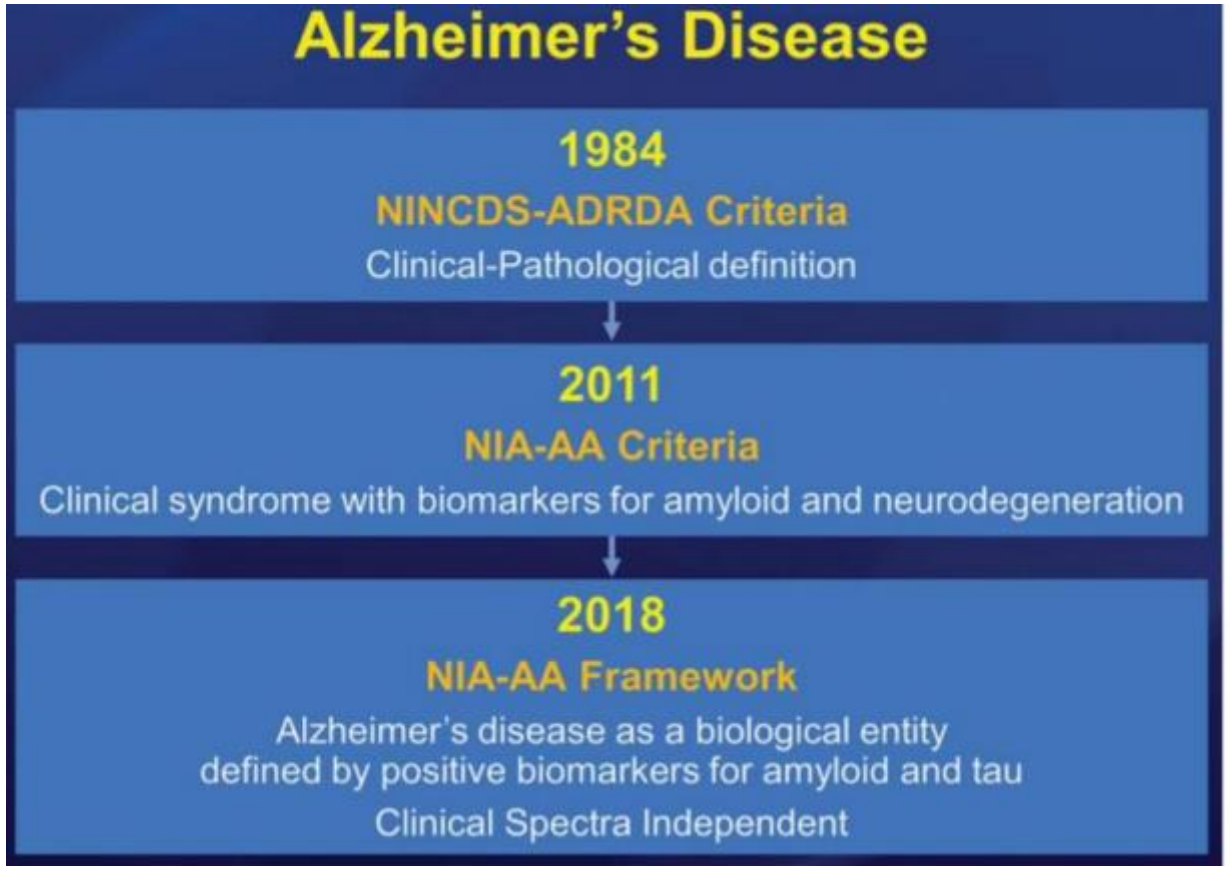
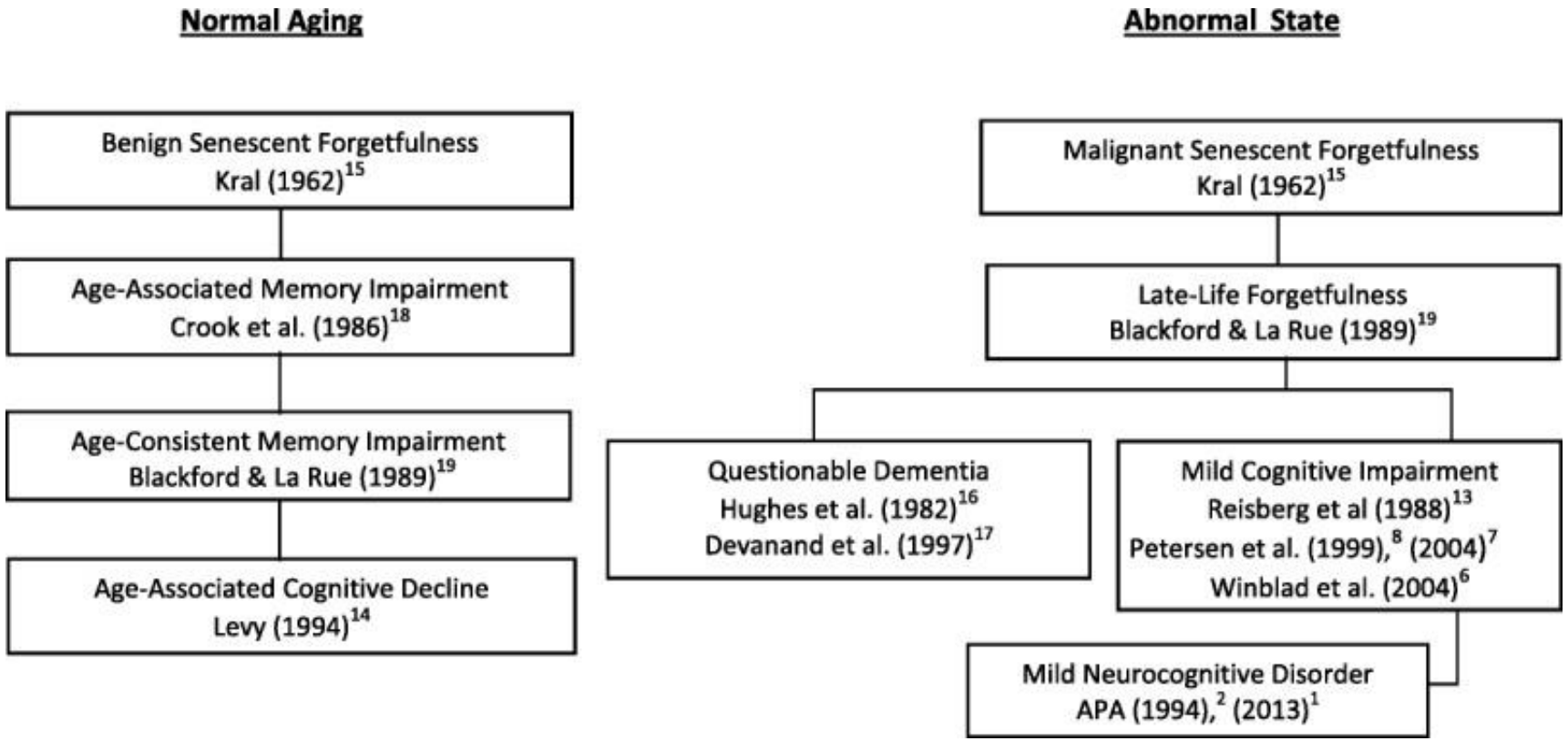
SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Associazione Geriatri Extraospedalieri



Dal 1906 ad oggi sono stati rivisti i criteri di ricerca per AD e la malattia viene definita sulla base di specifici processi patologici discostandosi dall'approccio basato sull'osservazione dei sintomi clinici e sul deterioramento delle funzioni cognitive , funzionali e definendo la malattia sulla base della presenza in vivo di specifiche proteine tossiche mediante analisi biochimica o metodiche di neuroimaging



Stokin GB, et at. Harvard Review of Psychiatry 2015

Published Ahead of Print on March 28, 2018 as 10.1212/WNL.0000000000005303

VIEWS & REVIEWS

Resistance vs resilience to Alzheimer disease

Clarifying terminology for preclinical studies

Neurology® 2018;0:1-9. doi:10.1212/WNL.0000000000005303

Eider M. Arenaza-Urquijo, PhD, and Prashanthi Vemuri, PhD

2 distinct mechanisms:
coping with pathology vs avoiding pathology

RESILIENZA

RESTARE SANI ANCHE IN PRESENZA di AD pathology

RESISTENZA

RESTARE SANI IN ASSENZA di AD pathology

Brain Imaging Behav. 2017 April ; 11(2): 383–390. doi:10.1007/s11682-016-9640-4.

Cognitive Resilience in Clinical and Preclinical Alzheimer's Disease: The Association of Amyloid and Tau Burden on Cognitive Performance

Dorene M. Rentz, PsyD[1,2], Elizabeth C. Mormino, PhD[1], Kathryn V. Papp, PhD[1,2], Rebecca A. Betensky, PhD[3], Reisa A. Sperling, MD[1,2,4], and Keith A. Johnson[1,2,4,5]

These findings imply that CR may be protective against early AD processes and enable some individuals to remain cognitively stable despite elevated tau and Aβ burden.

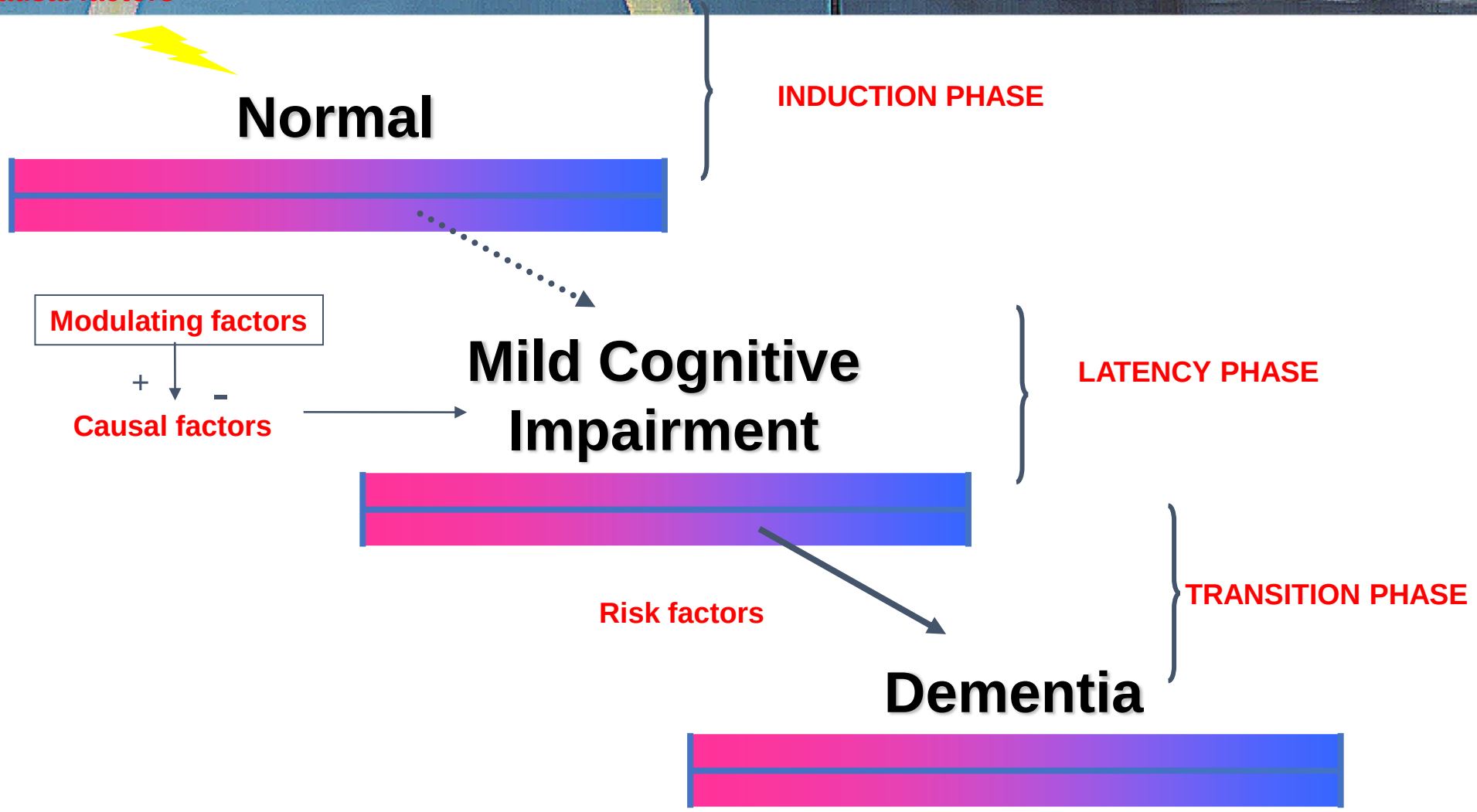
RISERVA COGNITIVA: FATTORE PROTETTIVO NEI CONFRONTI DELLO SVILUPPO DI AD

PLASTICITA' NEURONALE

ANCHE IN PRESENZA DI ALTE CONCENTRAZIONI DI CARICO AMILOIDEO O DI TAU

RISERVA COGNITIVA / PLASTICITA' : STILE DI VITA?

CONTINUUM COGNITIVO ????



Petersen 2001, modif.

- **Complex entity - Phenotypically heterogeneous - No certitude of conversion**

MCI Issues

- Subjective memory impairment
- Pathological performances (corrected for age and education level) following memory tests
- No interference of memory impairment on working, social and daily functions
- Other cognitive functions unimpaired
- Absence of other diseases able to explain memory impairment

(Petersen et al. 1995)

MCI: inquadramento diagnostico

- Prevenzione del rischio cardio-cerebro vascolare
- Promozione di stili di vita attivi
- **Ruolo del supporto farmacologico**

La combinazione armonica dei tre punti sopra citati è la chiave per un possibile *outcome*

Oxidative Stress: Endothelial Dysfunction and CAD/Renal Risk Factors

Oxidative stress and the CNS

Carbonylation and nitration of proteins
Peroxidation of membrane lipids
Mitochondrial DNA and nuclear oxidation
RNA oxidation

Diabetes
Smoking
LDL
Homocysteine
Estrogen deficiency
Hypertension

⇧ O_2
⇧ H_2O_2
Endothelial Cells and Vascular Smooth Muscle

Mitochondrial dysfunction

Endothelial Dysfunction

ALS
Parkinson's disease
Alzheimer's disease
Huntington's disease
Vascular Cognitive Impairment

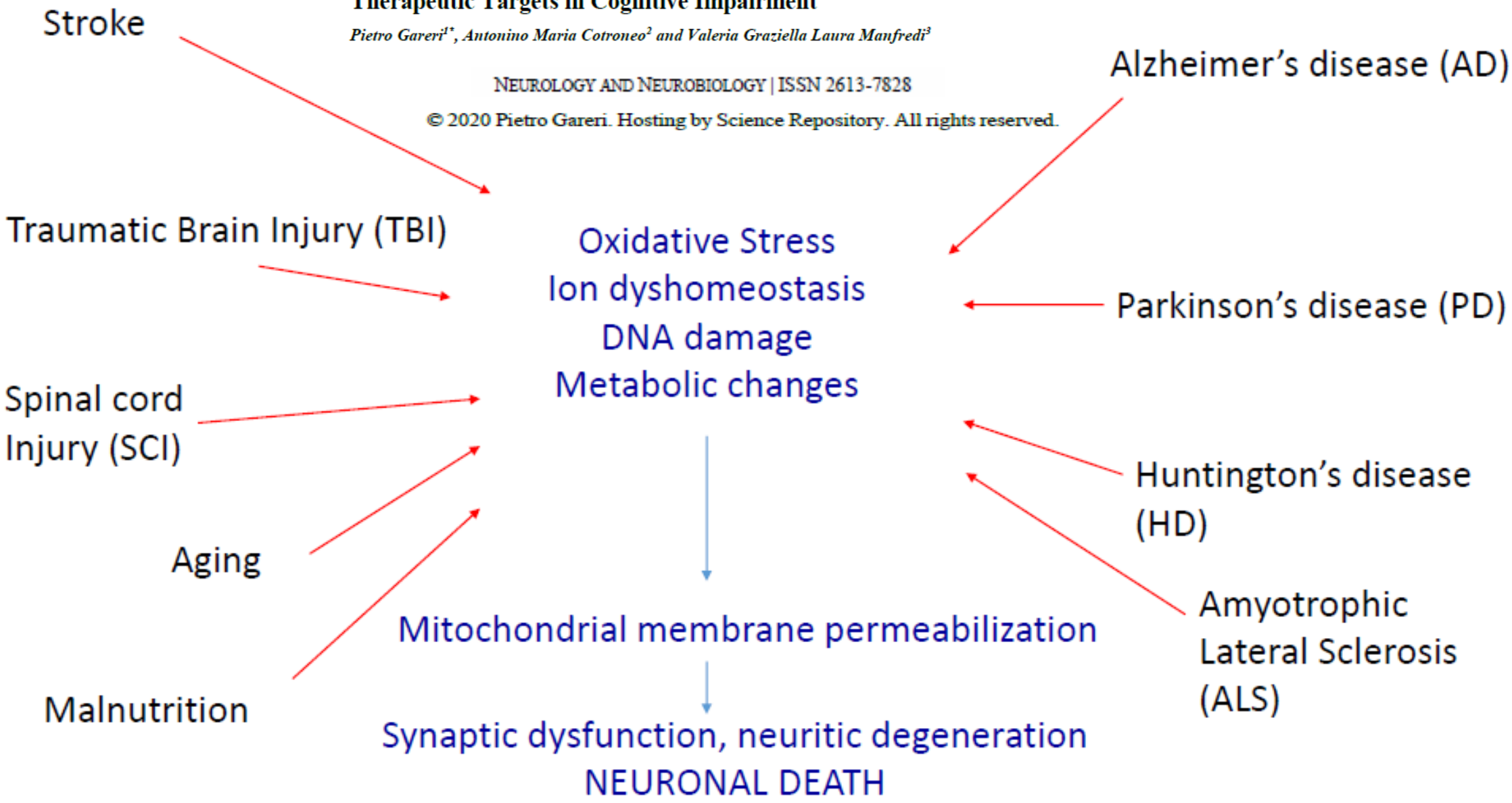
Apoptosis
Leukocyte adhesion
Lipid deposition
Vasoconstriction
VSMC growth
Thrombosis

Review Article

From Neuroinflammation to Neuroprotection: Focus on Potential New Therapeutic Targets in Cognitive Impairment

Pietro Gareri[1], Antonino Maria Cotroneo[2] and Valeria Graziella Laura Manfredi[3]*

NEUROLOGY AND NEUROBIOLOGY | ISSN 2613-7828



Review Article

From Neuroinflammation to Neuroprotection: Focus on Potential New Therapeutic Targets in Cognitive Impairment

Pietro Gareri[1], Antonino Maria Cotroneo[2] and Valeria Graziella Laura Manfredi[3]*

Grand Canyon Effect

Neuroprotection and Neurorescue in Neurodegenerative diseases

Neurodegenerative diseases
(AD, PD, HD, ALS)

Healthy habits

Food
- Red wine
- Blueberries
- Green tea
- Mediterranean diet

Exercise

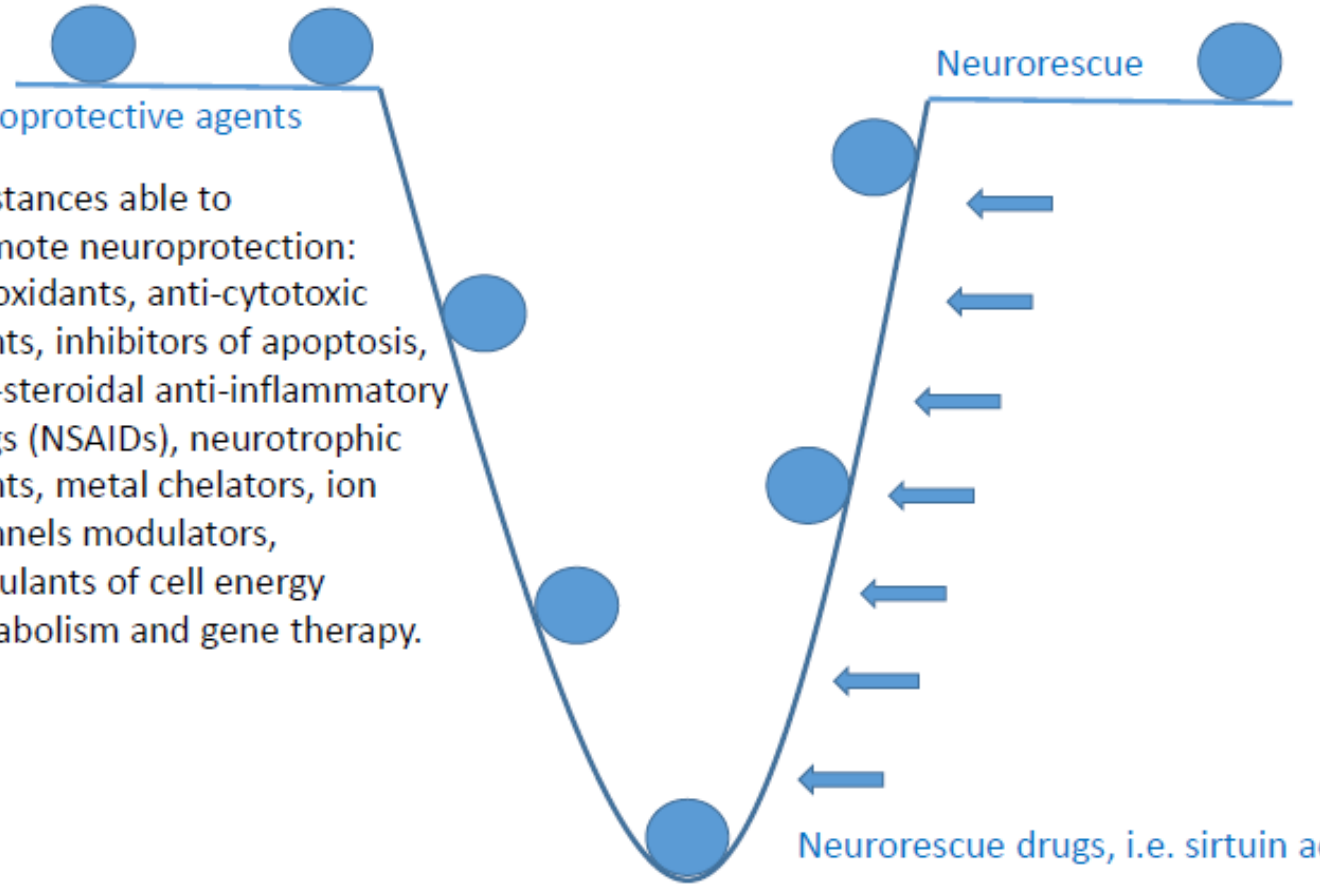
Role on:
- Neurogenesis
- Angiogenesis
- Neuroplasticity

Intellectual Activities

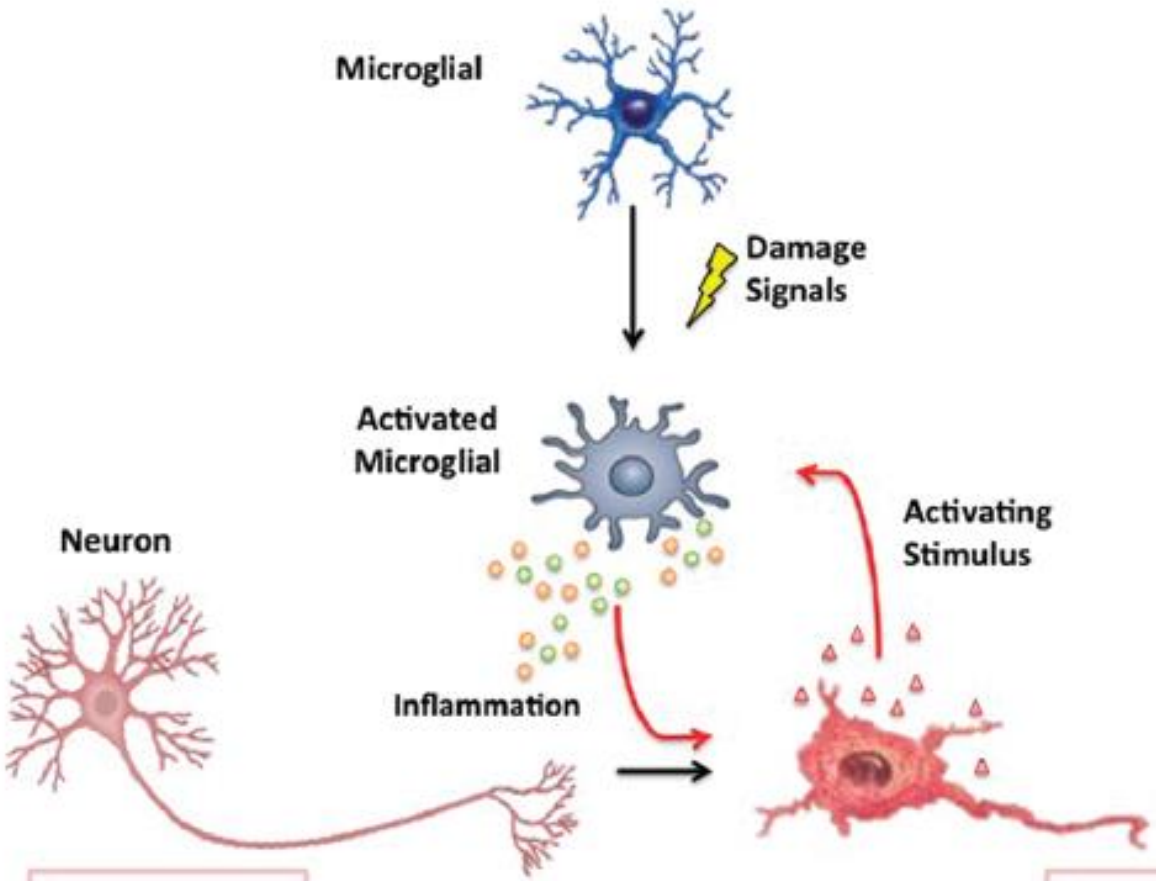
Role on:
- Synaptogenesis
- Neuroplasticity

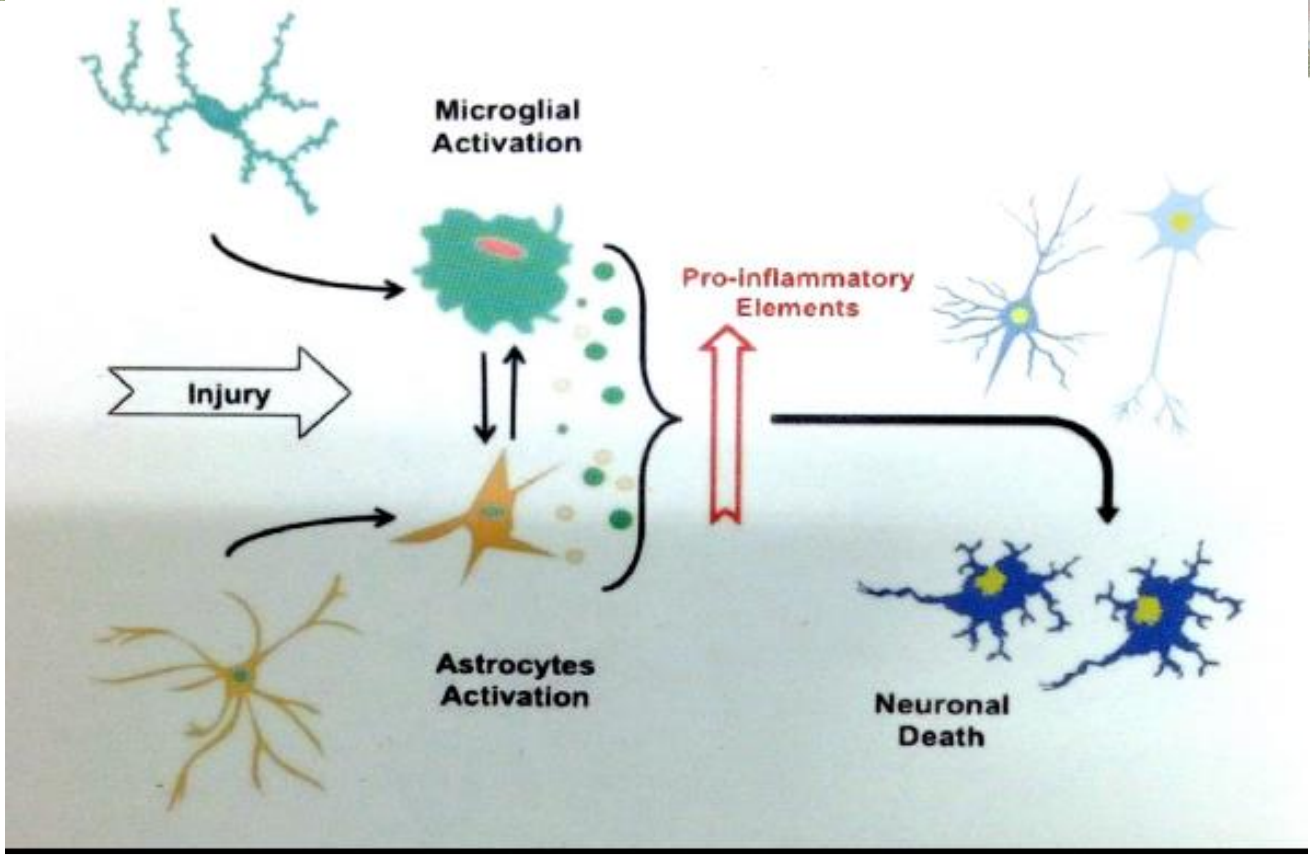
Neuroprotective agents

Substances able to promote neuroprotection: antioxidants, anti-cytotoxic agents, inhibitors of apoptosis, non-steroidal anti-inflammatory drugs (NSAIDs), neurotrophic agents, metal chelators, ion channels modulators, stimulants of cell energy metabolism and gene therapy.



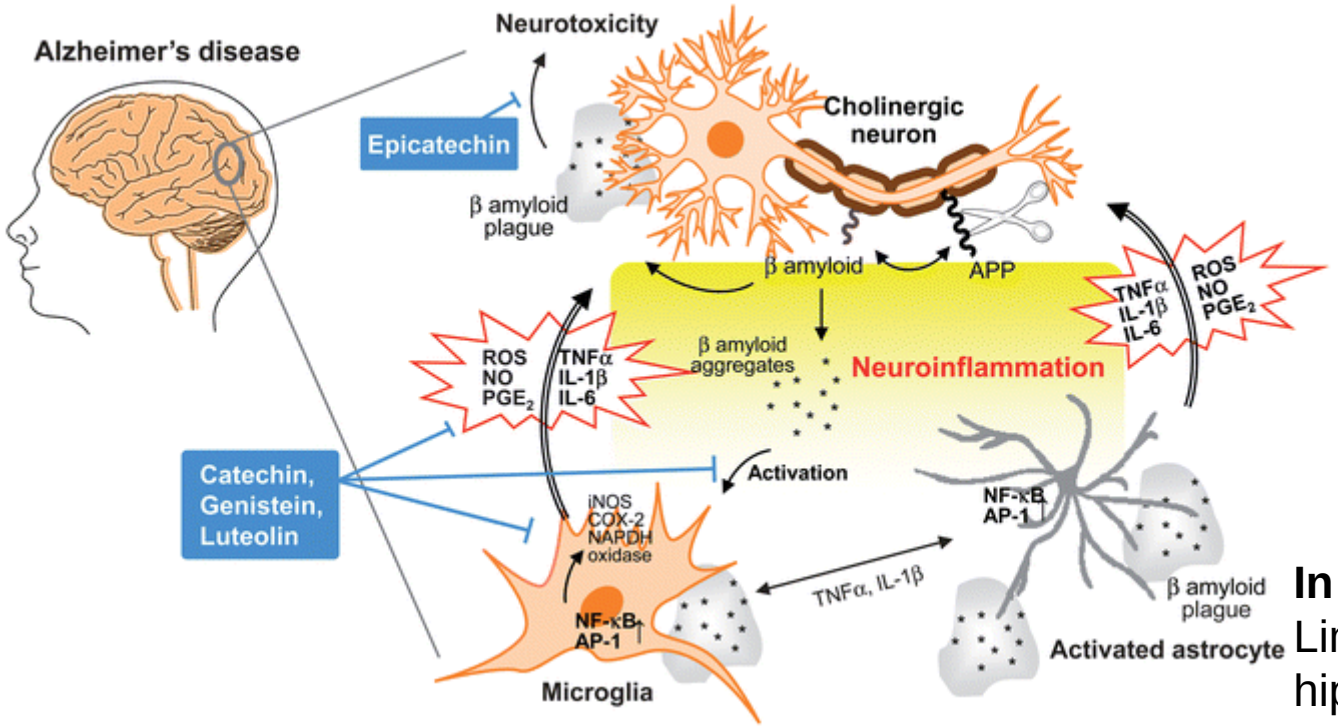
Microglia the working class cell of the brain





Vascular CI / post stroke CI

The mechanism by which Aβ induces inflammation and cell death is unclear but may
involve a complex cascade of biochemical events resulting in the imbalance of intracellular ions, production of inflammatory mediators and free radicals, and finally, apoptotic cell death that culminates in massive atrophy of susceptible areas



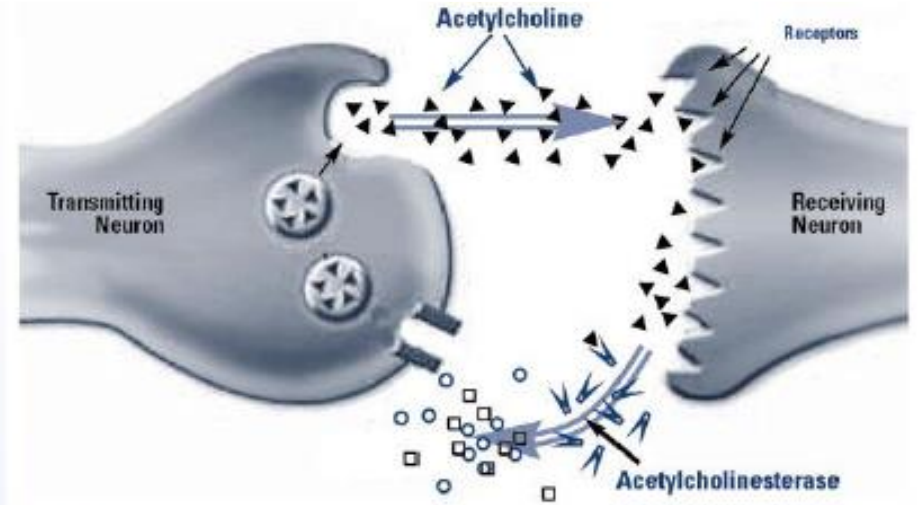
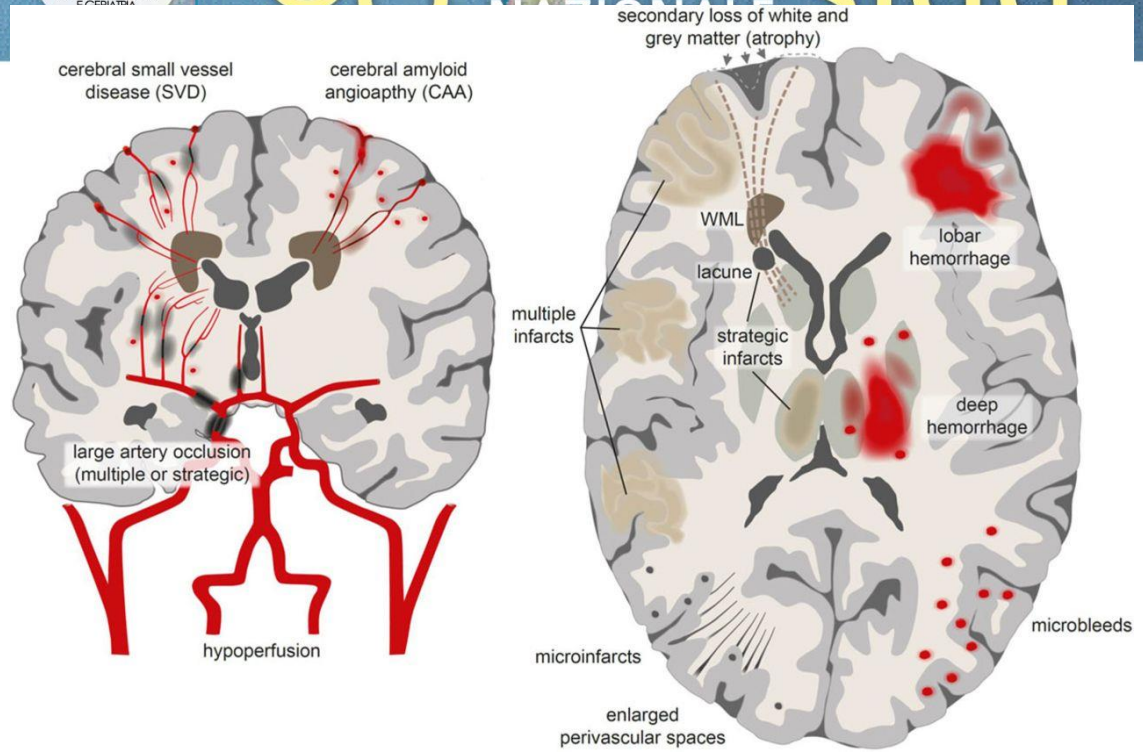


Fig. 1. After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.

In particular cholinergic neurons and pathways…
Limbic areas, medial part of temporal lobe, entorhinal cortex, hippocampus and amygdala, nBM and vertical band of Broca.
NA neurons involved too and the LC

Major mechanisms underlying vascular cognitive impairment (VCI)



A, Vascular causes. **B**, Brain parenchymal lesions associated with VCI.
(graphical realization: Antonia Weingart, Institute for Stroke and Dementia Research).

Circulation Research February 3, 2017

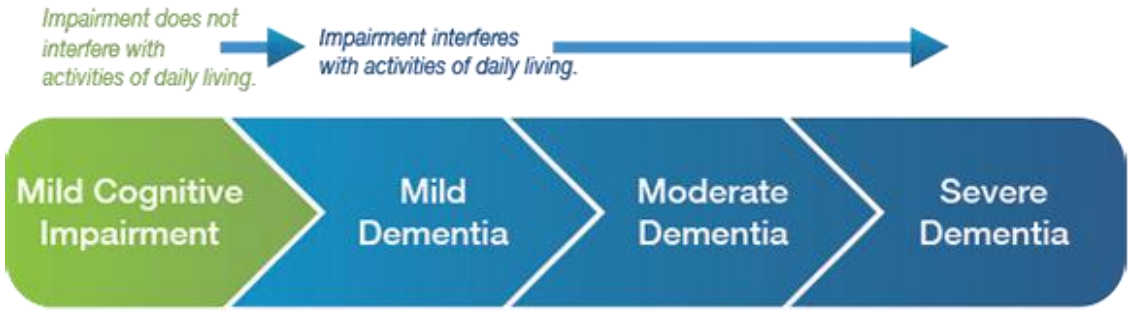
Vascular Cognitive Impairment

Vascular brain injury involving regions important for **memory**, **cognition** and **behavior**

Vascular **Mild CI**

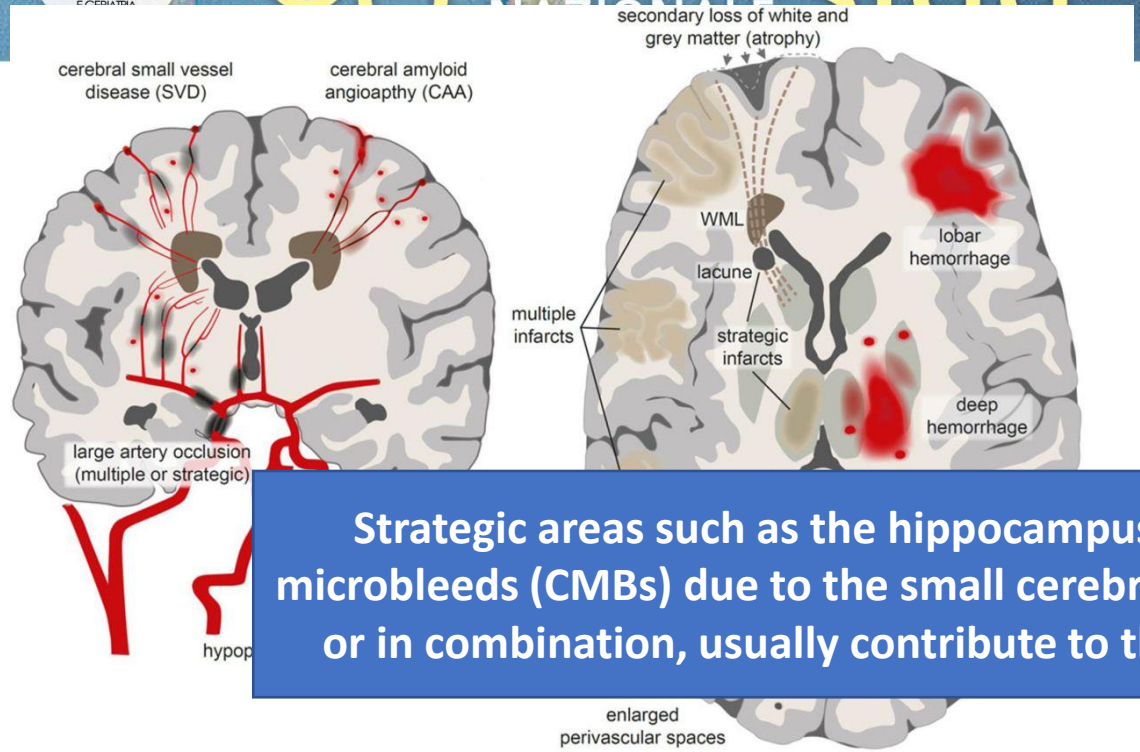
"**Mixed disease**": concomitant vascular and other pathology, such as pathology associated with AD

"pure" **Vascular Dementia** (VaD) and post-stroke dementia



In the Framingham study, stroke doubled the risk of dementia and poststroke cognitive decline is more common than stroke recurrence.

Major mechanisms underlying vascular cognitive impairment (VCI)



A, Vascular causes. **B**, Brain parenchymal lesions associated with VCI.
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Circulation Research February 3, 2017

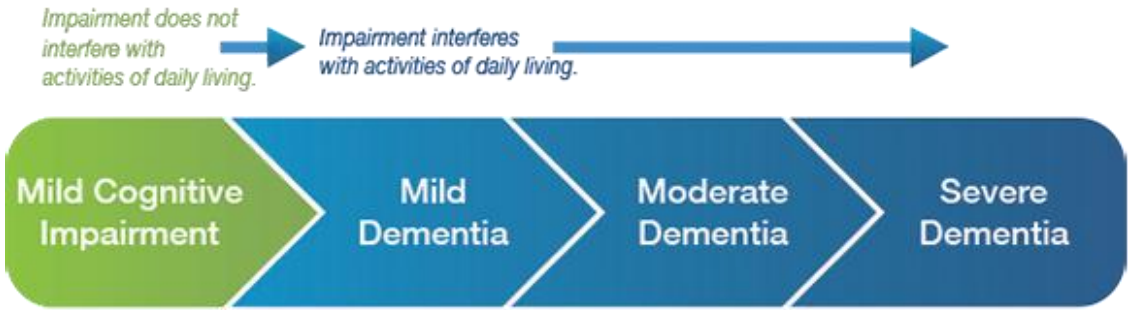
Vascular Cognitive Impairment

Vascular brain injury involving regions important for **memory**, **cognition** and **behavior**

Strategic areas such as the hippocampus and the white matter lesions (WMLs), the cerebral microbleeds (CMBs) due to the small cerebrovascular diseases and the mixed AD with stroke, alone or in combination, usually contribute to the pathogenesis of post-stroke cognitive impairment.

comitant
thology, such
ed with AD

"pure" **Vascular Dementia** (VaD)
and post-stroke dementia



In the Framingham study, stroke doubled the risk of dementia and poststroke cognitive decline is more common than stroke recurrence.

Possible treatments

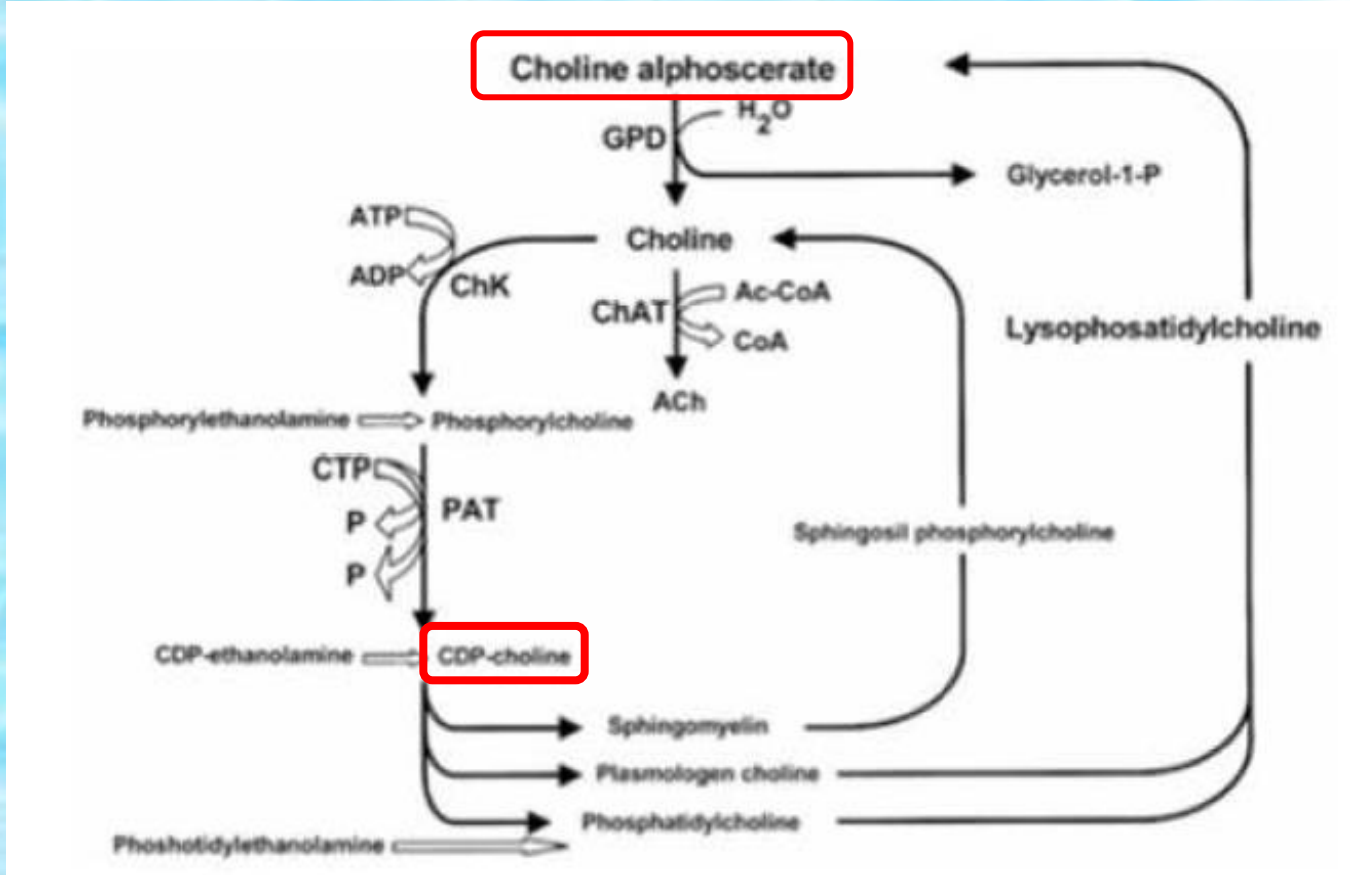
The pharmacological treatments must be started as soon as possible

- Antioxidants (vitamins C and E), L-acetyl-carnitine, Ginkgo Biloba
- MAO-B inhibitors (L-deprenyl)

- Homotaurine, palmytoylethanolamide + luteolin

- **Acetylcholine precursors (choline alphoscerate, citicoline)** have been shown to be effective in MCI and in dementia, both Alzheimer's and mixed dementia (see the ASCOMALVA, the IDEALE, the CITIRIVAD and CITICHOLINAGE studies)

Choline and the choline-containing phospholipid phosphatidylcholine are essential for maintaining cell membrane integrity and structure.



Modified from: Abbiati et al., 1991

Choline is probably one of the most basic nutrients necessary for optimal cognitive function being the precursor for acetylcholine and is also used by cellular machinery for synthesizing phosphatidylcholine

Editorial > Nutrients. 2023 Jun 27;15(13):2900. doi: 10.3390/nu15132900.

Choline: An Essential Nutrient for Human Health

Milagros Gallo [1 2], Fernando Gámiz [1]

Affiliations + expand

PMID: 37447226 PMCID: PMC10343572 DOI: 10.3390/nu15132900

Free PMC article

Abstract

Choline is an essential nutrient that plays a role in the synthesis of the phospholipid membrane, critical for cell functions, and it is the major source of methyl donors relevant for epigenetic modifications of the genome [...].

Randomized Controlled Trial > Eur J Nutr. 2022 Feb;61(1):219-230.
doi: 10.1007/s00394-021-02637-6. Epub 2021 Jul 21.

Differential metabolism of choline supplements in adult volunteers

Katrin A Böckmann [1], Axel R Franz [2 3], Michaela Minarski [2], Anna Shunova [2], Christian A Maiwald [2], Julian Schwarz [2], Maximilian Gross [2], Christian F Poets [2], Wolfgang Bernhard [2]

Affiliations + expand

PMID: 34287673 PMCID: PMC8783899 DOI: 10.1007/s00394-021
Free PMC article

> Aging Cell. 2019 Dec;18(6):e13037. doi: 10.1111/acel.13037. Epub 2019 Sep 27.

Lifelong choline supplementation ameliorates Alzheimer's disease pathology and associated cognitive deficits by attenuating microglia activation

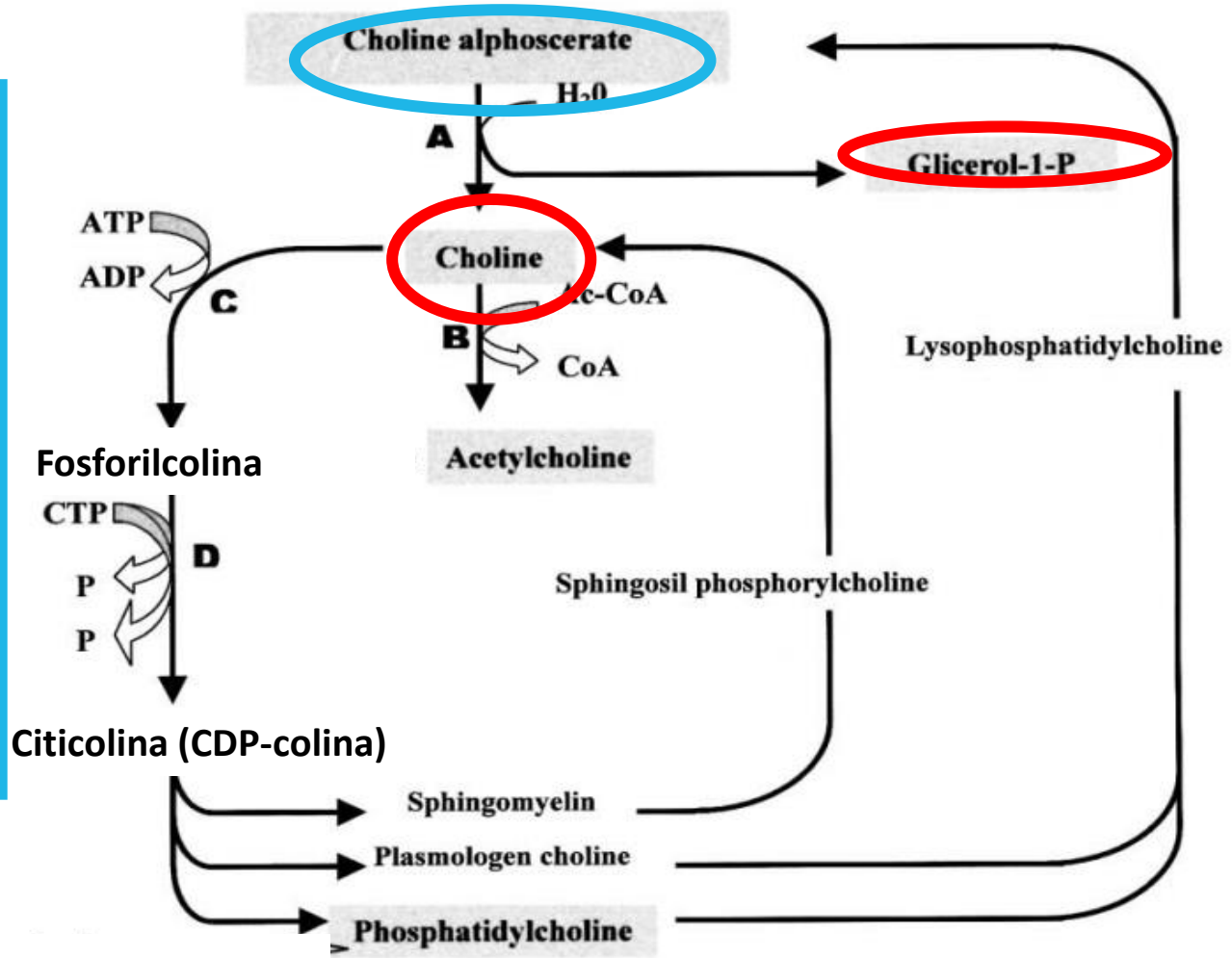
Ramon Velazquez [1], Eric Ferreira [1], Sara Knowles [1 2], Chaya Fux [1], Alexis Rodin [1], Wendy Winslow [1], Salvatore Oddo [1 2]

Affiliations + expand

PMID: 31560162 PMCID: PMC6826123 DOI: 10.1111/acel.13037
Free PMC article

La colina alfoscerato fornisce colina e glicerolo-1-fosfato

A) La colina alfoscerato viene trasformata da un enzima in una molecola di **COLINA** e in una di **glicerolo-1-fosfato** (che dopo essere stato fosforilato entra nel pool dei fosfolipidi)

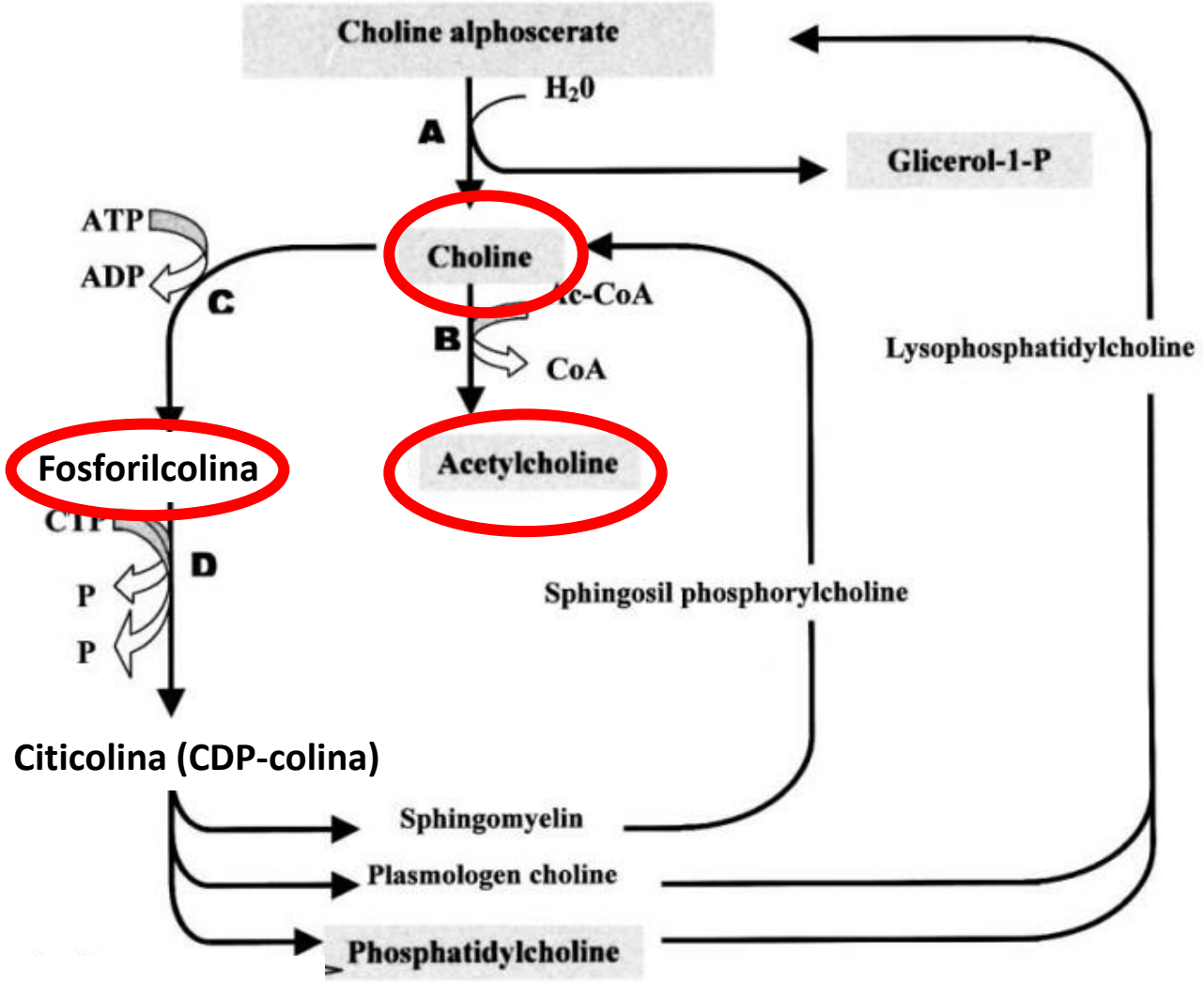


Traini E et al. Curr Alzheimer Res. 2013 Dec;10(10):1070-9;
Amenta F et al. Mech Ageing Dev. 2001 Nov;122(16):2025-40

La colina viene trasformata in:

B) acetilcolina

C) fosforilcolina



Traini E et al. Curr Alzheimer Res. 2013 Dec;10(10):1070-9;
Amenta F et al. Mech Ageing Dev. 2001 Nov;122(16):2025-40

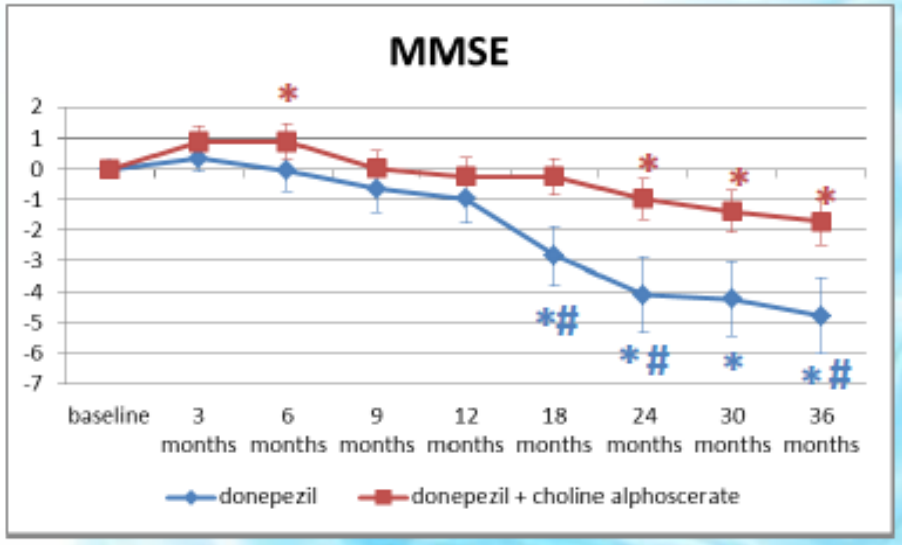
J Alzheimers Dis. 2014;42 Suppl 3:S281-8. doi: 10.3233/JAD-140150.

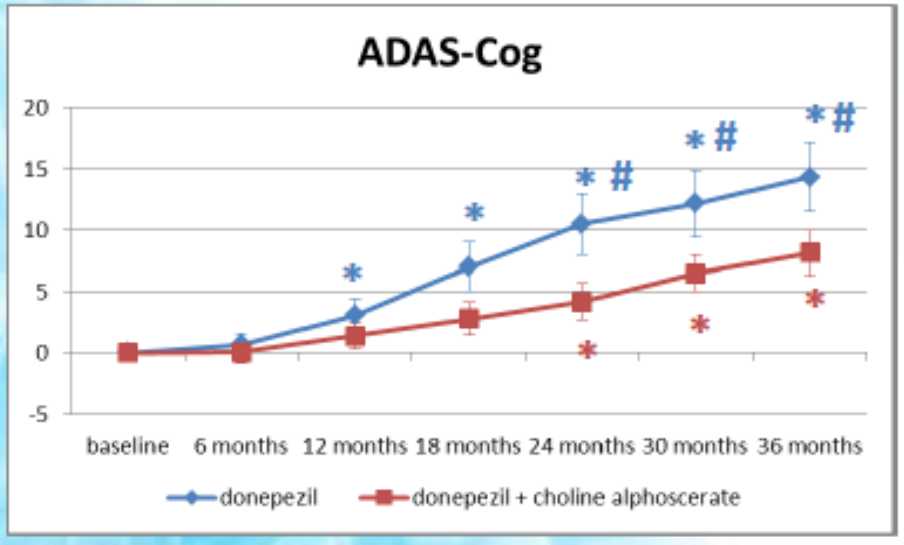
The ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease) Trial: interim results after two years of treatment.

Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E.

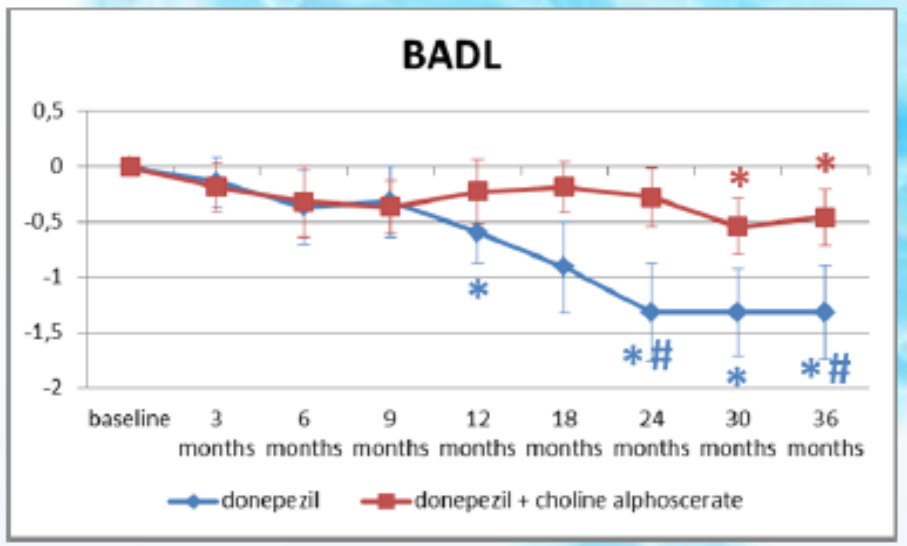
Cholinesterase inhibitors (ChE-Is) are used for symptomatic treatment of mild-to-moderate Alzheimer's disease (AD), but long-term effects of these compounds are mild and not always obvious. Preclinical studies have shown that combination of ChE-Is and the cholinergic precursor choline alphoscerate increases brain acetylcholine levels more effectively than single compounds alone. ASCOMALVA (Effect of association between a ChE-I and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury) is a double-blind trial investigating if the ChE-I donepezil and choline alphoscerate in combination are more effective that donepezil alone. The trial has recruited AD patients suffering from ischemic brain damage documented by neuroimaging and has completed 2 years of observation in 113 patients of the 210 planned. Patients were randomly allotted to an active treatment group (donepezil + choline alphoscerate) or to a reference group (donepezil + placebo). Cognitive functions were assessed by the Mini-Mental State Evaluation and Alzheimer's Disease Assessment Scale Cognitive subscale. Daily activity was evaluated by the basic and instrumental activities of daily living tests. Behavioral symptoms were assessed by the Neuropsychiatric Inventory. Over the 24-month observation period, patients of the reference group showed a moderate time-dependent worsening in all the parameters investigated. Treatment with donepezil plus choline alphoscerate significantly slowed changes of the different items analyzed. These findings suggest that the combination of choline alphoscerate with a ChE-I may prolong/increase the effectiveness of cholinergic therapies in AD with concomitant ischemic cerebrovascular injury.

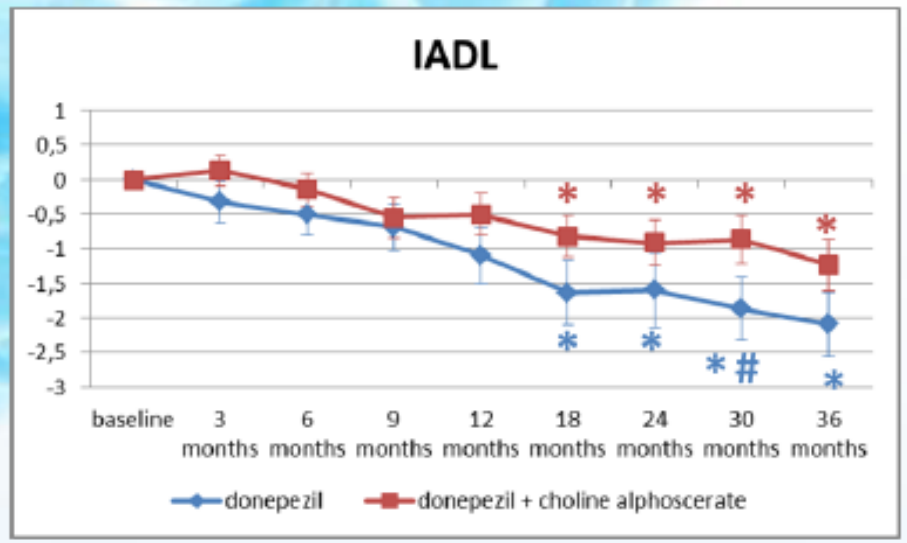
Valutazione del Declino cognitivo





Valutazione funzionale





I dati sono la media ± S.E.M. * : p <0,05 *vs.* baseline # : p <0,05 *vs.* terapia associativa

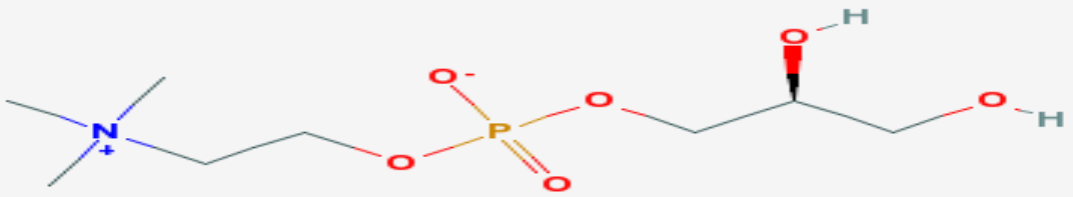
Amenta et al., 2014

Citicolina e Colina alfoscerato a confronto

COLINA ALFOSCERATO

(glicerilfosforilcolina)

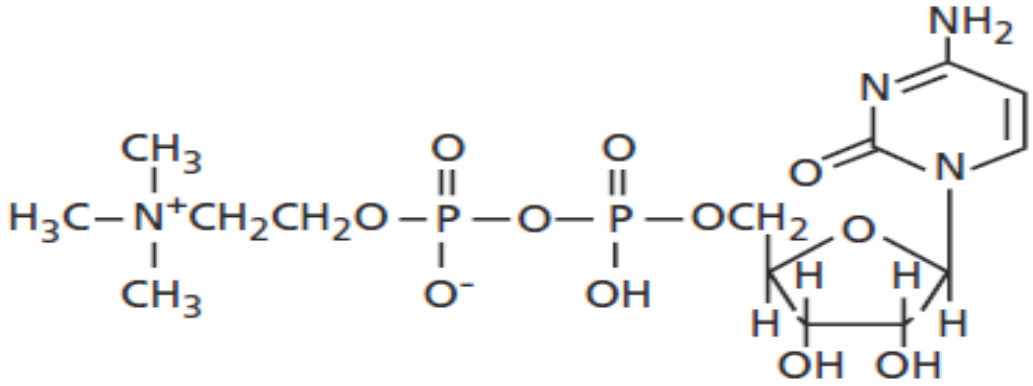
Struttura chimica di colina alfoscerato (contenente il 40,5% di colina) che è trasportatore di colina (nutriente essenziale).



Molecular Formula	$C_8H_{20}NO_6P$

CITICOLINA, colina-citidina-5'difosfato sale sodico

La citicolina è un intermedio chiave della biosintesi della fosfatidilcolina *che è uno dei più importanti componenti delle membrane biologiche, comprese le neuronali.*



Citicolina e Colina bitartrato a confronto

La colina bitartrato, come la colina alfoscerato, è un sale di colina (apporta il 40% di colina)

European Food Safety Authority

EFSA Journal 2013;11(10):3421

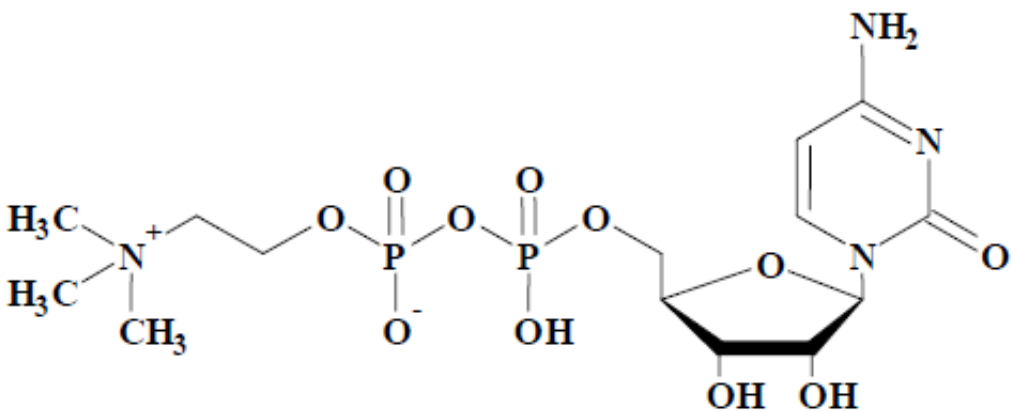
SCIENTIFIC OPINION

Scientific Opinion on the safety of "citicoline" as a Novel Food ingredient[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

Figure 1: Chemical Structure of Citicoline



- CDP-choline (cytidine-5'-diphosphate-choline) is an endogenous compound normally produced by the body
- When it is introduced as a drug, it can be called citicoline

- Citicoline:
  - inhibits apoptosis associated with cerebral ischemia
  - inhibits several models of neurodegeneration
  - is able to potentiate neuroplasticity
  - is a natural precursor of phospholipid synthesis, chiefly phosphatidylcholine or rather serves as choline source in the metabolic pathways for biosynthesis of acethylcholine
  - pharmacokinetic studies suggested that it is well absorbed and highly bioavailable with oral dosing.

Gareri , Cotroneo et al., Clin Interv Aging 2015

CDP-choline (citicoline)

Cytidine → Uridine phosphate → **Cytidine triphosphate**

Cytidine triphosphate → CTP-cytidylyltransferase

1,2-diacylglycerol

Choline → Phospho-choline → **Citicoline** → Phosphatidyl-choline

- **Oral Bioavailability greater than 90%**
- **Metabolism**
- **Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second peak at 24 hours post-dosing**

Choline → Betaine → Methionine → S-adenosyl-L-methionine

S-adenosyl-L-homocysteine → Cysteine → Glutathione

Adibhatla et al., Stroke, 2001, modified

Citicolina: meccanismo di azione

Colina citidina –5'- difosfato

↓ Attività della PLA2 (fosfolipasi A2)

↑ Sintesi della PC (fosfatidilcolina)

↓ Acido arachidonico

↓ Lisofosfatidilcolina

↓ Radicali liberi

↓ Sfingomielinasi

↑ **CCT** (CTP-fosforilcolina-citidiltransferasi), **enzima chiave della sintesi della PC**

↓ **Perossidazione lipidica**

Preservazione sfingomielina

Table I Clinical use of citicoline

- Cerebrovascular disease
- Head trauma of varying degrees
- Cognitive disorders of diverse etiology
- Glaucoma
- Ambliopia
- Parkinson's disease

Clin Interv Aging. 2013; 8:1321-7

- **CDP-choline** (cytidine-5′-diphosphate choline), also called citicoline, is one of the most frequently prescribed drugs for cognitive impairment in several European countries
- It is composed of ribose, pyrophosphate, cytosine (a nitrogenous base), and choline
- Citicoline is effective in CI of diverse etiology, such as in CI following cerebrovascular disease

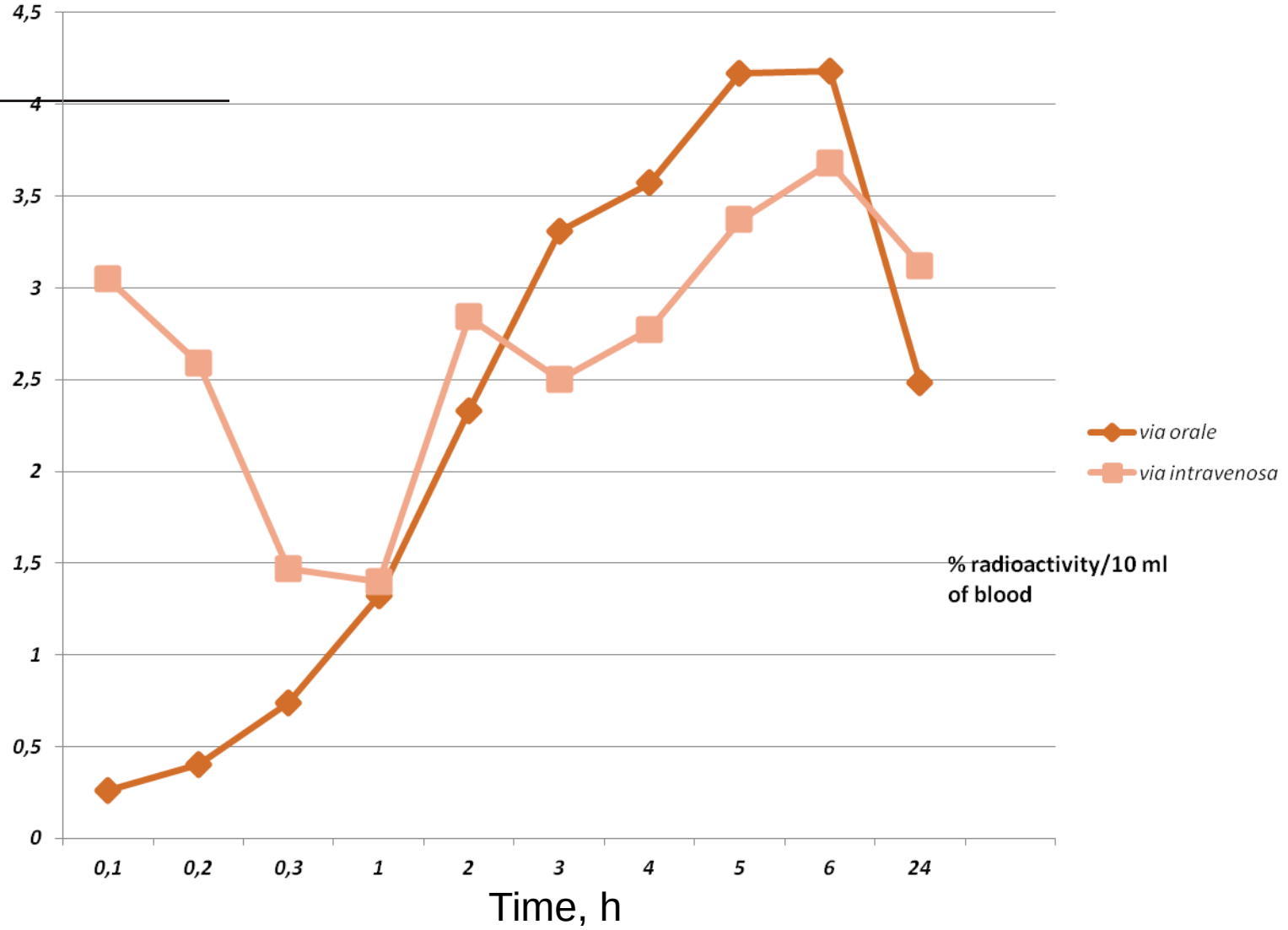


Table 2 Main neuroprotective effects of citicoline

Ischemic cascade level	Citicoline putative mode of action	Main effects	References
Cell energy balance	Stimulation/restoration of Na^+/K^+ ATPase activity	Cell energy deficiency correction Preservation/restoration of neuronal ionic balance	Plataris et al[45]
	Restoration/prevention of loss of neuronal ATP levels	Preservation/restoration of membrane integrity	Hurtado et al[34]
Glutamate exitotoxicity	Delay/prevention in the reversal of neuronal glutamate transporters	Decreased/delayed neuronal glutamate efflux	Hurtado et al[34]
	Increase in the surface fraction of EAAT2 transporter	Increased glutamate uptake by astrocytes	Hurtado et al[31]
Oxidative cascade	Prevention of PLA2 activation	Decreased FFA release	Adibhatla and Hatcher[46]
	Induction of glutathione reductase activity	Glutathione synthesis stimulation	Adibhatla et al[48]
Apoptosis	Increase in the Bcl-2 expression	Attenuation/neutralization of Bad/Bax family proteins	Sobrado et al[72]
	Upregulation of SIRT1 protein	Attenuation/prevention of caspase-3 activation	Hurtado et al[78]
	Downregulation of procaspase and caspase expression	Attenuation/prevention of PARP cleavage and DNA damage	Krupinski et al[69]
Endothelial barrier disruption	TJ protein regulation	Reduction of brain edema	Schabitz et al[30]
		Decrease in permeability of endothelial barrier and restoration of TJ proteins linear structure	Ma et al[49]

Abbreviations: EAAT2, excitatory amino acid transporter 2; PLA2, phospholipase 2; FFA, free fatty acids; PARP, poly (ADP-ribose) polymerase; TJ, tight junctions.

Martinov and Gusev, J Exp Pharmacol, 2015

Table 3 Main neuroregenerative/neurorestorative effects of citicoline

Structure/ function	Type of study (experimental/clinical)	Citicoline main effects	References
Neuronal morphology	Experimental, rats	Enhanced dendritic arborization and morphology of neurons	Hurtado et al[97] Rema et al[98]
Neurogenesis	Experimental, rats	Increase in migratory neuronal response from SVZ and DG to PI area	Diederich et al[92]
		Increased neurogenesis in the PI area	Gutierrez-Fernandez et al[77]
Synaptogenesis	Experimental, rats	Synaptophysin upregulation in the PI area	Gutierrez-Fernandez et al[77]
Gliagenesis	Experimental, rats	Decreased GFAP levels in the PI area	Gutierrez-Fernandez et al[77]
Angiogenesis	Experimental, rats	Increased expression of CD 105 positive cells in PI area	Krupinski et al[70]
	Experimental, rats	Increased expression of VEGF in the PI area	Gutierrez-Fernandez et al[77]
Neurotransmitter metabolism	Experimental, mice	Citicoline enhances K^+ induced release of DA	Agut et al[107]
	Experimental, rats	Dose-dependent increase in DA and ACh receptor densities	Gimenez et al[93]
	Experimental, rats	Increased ACh synthesis	Kakihana et al[29]
	Clinical, ^{1}H-MR spectroscopy	Increase in NAA and Cho levels	Yoon et al[111]
	Clinical, ^{31}P-MR spectroscopy	Dose-dependent increase in PCr and β-NTP	Silvery et al[94]

Abbreviations: SVZ, subventricular zone; DG, dentatal gyrus; PI, peri-infarct; VEGF, vascular endothelial growth factor; DA, dopamine; ACh, acetylcholine; NAA, N-acetylaspartate; Cho, choline; PCr, phosphocreatine; β-NTP, beta-nucleoside triphosphates.

Martinov and Gusev, J Exp Pharmacol, 2015

Citicoline vs choline

Citicoline's therapeutic effects in such conditions stem from its ability to:

1)increase phosphatidylcholine synthesis, the primary component of neuronal membranes;

2)enhance acetylcholine synthesis, ameliorating the symptoms resulting from ischemic loss of cholinergic neurons;

3)promote the synthesis of several other membrane phospholipids, including phosphatidylethanolamine and phosphatidylserine, leading to repair and regeneration of axons and synapses; and

4)prevent the accumulation of free fatty acids and the generation of free radicals at the site of ischemia, thereby preventing the initiation of a proinflammatory cascade of events.

5)Thus, citicoline's therapeutic impact extends well beyond that of choline alone for the treatment of neurological conditions.

6)Choline in citicoline is less prone to conversion to trimethylamine (TMA), a gaseous metabolite oxidized in the liver to its atherogenic N-oxide TMAO

2018 *Natural Medicine Journal* (ISSN 2157-6769)

Neurol Sci. 2010 Dec 15;299(1-2):188-92. Epub 2010 Sep 27.

Citicoline, use in cognitive decline: vascular and degenerative.

García-Cobos R, Frank-García A, Gutiérrez-Fernández M, Díez-Tejedor E.

Source

- Citicoline improves both the immediate and the delayed recall of words and objects
- It ameliorated short and long-term memory, capacity of attention and perceptual-motor capacity, as well as behavioural and emotional control
- Improvement of verbal memory functioning in older individuals with relatively inefficient memory

medium and long-term on vascular cognitive impairment and Alzheimer's disease. **Results show that Citicoline seems to have beneficial impact on several cognitive domains**, but the methodological heterogeneity of the these studies makes it difficult to draw conclusions about these effects. New trials with a greater number of patients, uniform diagnostic criteria for inclusion and standardized neuropsychological assessment are needed to evidence with much more consistency Citicoline efficacy upon cognitive disorders. The use of new neuroimaging procedures in current trials could be of great interest.

Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly[1]

THE COCHRANE COLLABORATION®

14 clinical trials

N = 1291

In 2005, a Cochrane revision assessed the benefits of the treatment with citicoline in aged patients with chronic cerebral disorders .
This revision was based on 14 clinical trials with a total population of 1291 patients

In this revision it was concluded that the treatment with citicoline had a positive effect on memory, behavior and global impression in elderly patients suffering from cognitive deficits associated with chronic cerebral disorders mainly related with cerebrovascular diseases

Citicoline has a positive effect on memory and behavior in elderly patients suffering from cognitive deficits associated with cerebrovascular diseases[1]

Global impression

Peto Odds Ratio
8.89 (5.19;15.22)

Formal meta-analysis
4 clinical trials

N= 217

Memory

Memory Measures
SMD: 0.38 (95% CI 0.11,0.65)
Memory Recall
SMD: 0.22 (95% CI 0.07,0.37)

Formal meta-analysis
6 clinical trials

N=675

Behaviour

Behavioural Measures
SMD: -0.60 (95% CI -1.05, -0.15)

Formal meta-analysis
8 clinical trials

N=844

- Sirtuins are NAD^+-dependent histone deacetylases
- SIRT1 is the best characterized sirtuin expressed in neurons
- SIRT1 is protective against acute and chronic neurological diseases
- Deacetylation on histone and non-histone targets contributes to the protective effects of SIRT1
- The activity of SIRT1 is adjustable, making it a neuroprotective target.

Protective effects in:

- **Alzheimer's disease**
- **Parkinson's disease**
- **Prion diseases**
- **Huntington's disease**
- **Amyotrophic Lateral Sclerosis**
- **Multiple Sclerosis**
- **Cerebral ischemia**

Protective effects and mechanisms of sirtuins in the nervous system

Feng Zhang[a,c,*], Suping Wang[a,c,*], Li Gan[b], Peter S. Vosler[c], Yanqin Gao[a,c], and Jun Chen[a,c,d]

Prog Neurobiol. 2011 November ; 95(3): 373–395.

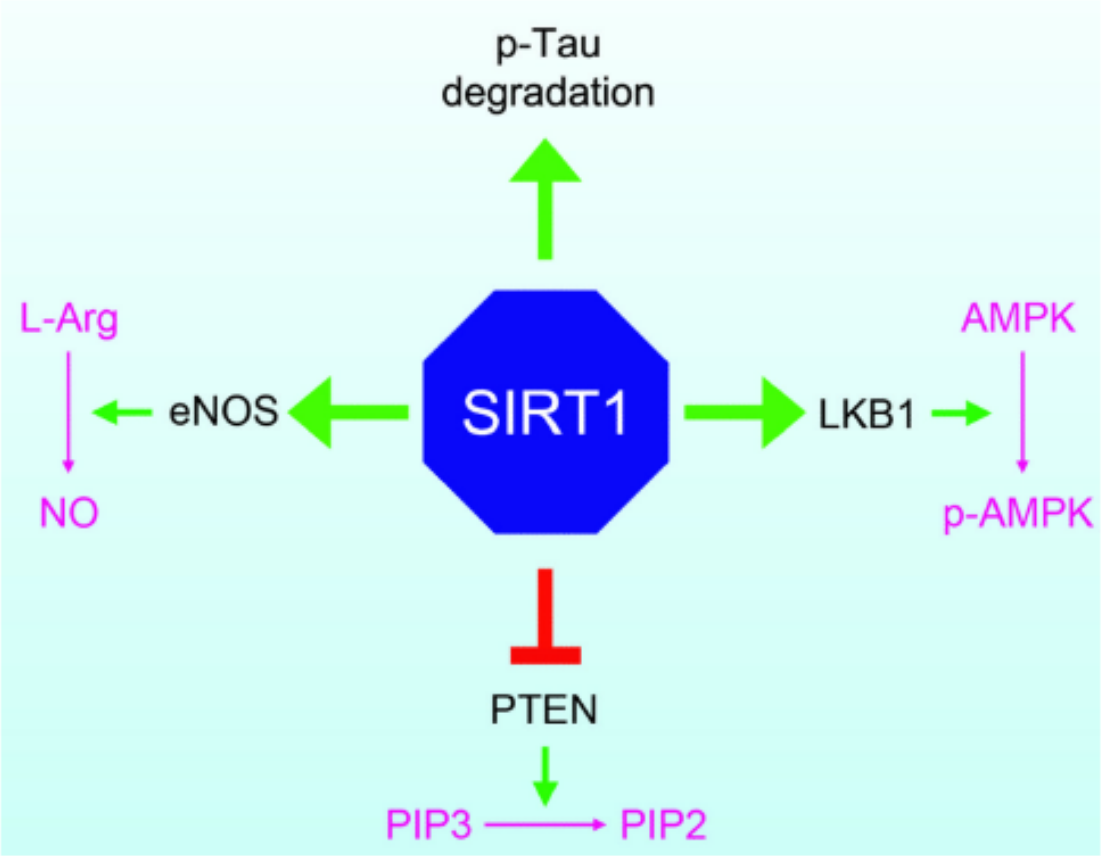


Figure 5. Cytosolic targets of SIRT1

In addition to its numerous actions in the nucleus, SIRT1 also has some newly discovered cytosolic targets. SIRT1 deacetylates and activates LKB1, leading to increased AMPK activity and attenuating ischemic brain injury. SIRT1 activity can also inhibit enzyme activity. Deacetylation of PTEN by SIRT1 inhibits the phosphatase's ability to bind and dephosphorylate PIP3, and results in unhindered activity of the neuroprotective PI3K/Akt signaling pathway. Deacetylation of eNOS stimulates the production of NO, a potent vasodilator. Putatively, this improves cerebral perfusion following ischemic stroke or subarachnoid hemorrhage. Finally, SIRT1 also deacetylates phosphorylated tau, facilitating its degradation and reducing neuronal death in models of Alzheimer's disease.

Prog Neurobiol. Author manuscript; available in PMC 2012 November 1.

Journal of Neurochemistry

JNC

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doi: 10.1111/jnc.12269

Citicoline (CDP–choline) increases Sirtuin1 expression concomitant to neuroprotection in experimental stroke

Olivia Hurtado,*[,1] Macarena Hernández-Jiménez,*[,1] Juan G. Zarruk,* María I. Cuartero,* Iván Ballesteros,* Guadalupe Camarero,* Ana Moraga,* Jesús M. Pradillo,† María A. Moro* and Ignacio Lizasoain*

Food and Nutrition Sciences, 2012, 3, 769-773
http://dx.doi.org/10.4236/fns.2012.36103 Published Online June 2012 (http://www.SciRP.org/journal/fns)
Scientific Research

Improved Attentional Performance Following Citicoline Administration in Healthy Adult Women

Erin McGlade[1,2], Allison Locatelli[1], Julia Hardy[1], Toshikazu Kamiya[3], Masahiko Morita[4], Koji Morishita[4], Yoichiro Sugimura[4], Deborah Yurgelun-Todd[1,2]

Table 1. Baseline subject demographics.

	250 mg (N = 20)	500 mg (N = 20)	Placebo (N = 20)
Age ± SD	46.00 ± 4.60	48.20 ± 5.99	47.95 ± 5.74
Education ± SD (years)	16.53 ± 2.37	17.75 ± 1.92	16.30 ± 2.54
Height (in) ± SD	64.22 ± 3.59	63.93 ± 2.28	64.30 ± 3.18
Weight (lbs) ± SD	158.38 ± 26.67	147.25 ± 40.15	154.80 ± 34.74
Vocabulary Score ± SD	105.15 ± 17.64	109.75 ± 11.48	103.60 ± 11.55

Our findings suggest that citicoline may improve attentional performance in middle-aged women and may ameliorate attentional deficits associated with central nervous system disorders

International Journal of *Molecular Sciences*

MDPI

Received: 21 January 2016; Accepted: 7 March 2016; Published: 16 March 2016

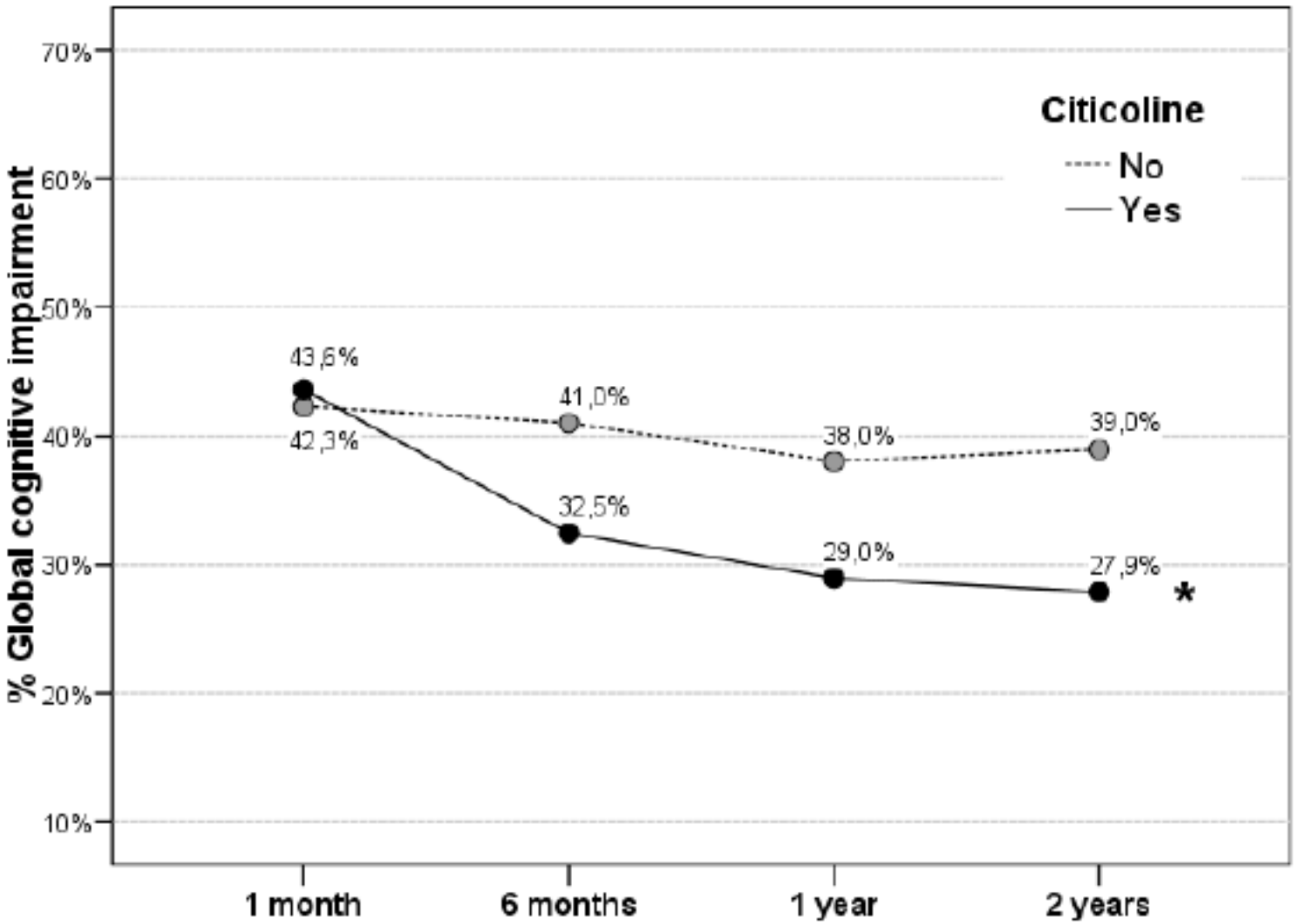
Article

Long-Term Treatment with Citicoline Prevents Cognitive Decline and Predicts a Better Quality of Life after a First Ischemic Stroke

Jose Alvarez-Sabín [1,*], Estevo Santamarina [1], Olga Maisterra [1], Carlos Jacas [2], Carlos Molina [1] and Manuel Quintana [1]

Abstract: Stroke, as the leading cause of physical disability and cognitive impairment, has a very significant impact on patients' quality of life (QoL). The objective of this study is to know the effect of citicoline treatment in Qol and cognitive performance in the long-term in patients with a first ischemic stroke. This is an open-label, randomized, parallel study of citicoline *vs.* usual treatment. All subjects were selected 6 weeks after suffering a first ischemic stroke and randomized into parallel arms. Neuropsychological evaluation was performed at 1 month, 6 months, 1 year and 2 years after stroke, and QoL was measured using the EuroQoL-5D questionnaire at 2 years. 163 patients were followed during 2 years. The mean age was 67.5 years-old, and 50.9% were women. Age and absence of citicoline treatment were independent predictors of both utility and poor quality of life. Patients with cognitive impairment had a poorer QoL at 2 years (0.55 *vs.* 0.66 in utility, $p = 0.015$). Citicoline treatment improved significantly cognitive status during follow-up ($p = 0.005$). In conclusion, treatment with long-term citicoline is associated with a better QoL and improves cognitive status 2 years after a first ischemic stroke.

International Journal of



d: 16 March 2016

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Abstract:

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$p = 0.015$). Citicoline treatment improved significantly cognitive status during follow-up ($p = 0.005$). In conclusion, treatment with long-term citicoline is associated with a better QoL and improves cognitive status 2 years after a first ischemic stroke.

- **THE FUTURE PERSPECTIVES**

- **The CITICHOLINAGE Study**

- **The CITIRIVAD Study**

- **The VITA Study– The IDEALE Study**

1) **Why does citicoline work?**
2) **What are its main mechanisms of action?**
3) **Why chronic administration?**
4) **Focus on the three studies**

- **Phospholipids (PC, PE, PS)**
- **Neurotransmitters (Ach, DA, NA)**
- **Neuroprotective and oxidative stress**

(sirtuin-1, glutathione synthesis)

- **Mytochondrial dysfunction (cardiolipin)**
- **Glutamate**
- **Synaptogenesis, gliagenesis**

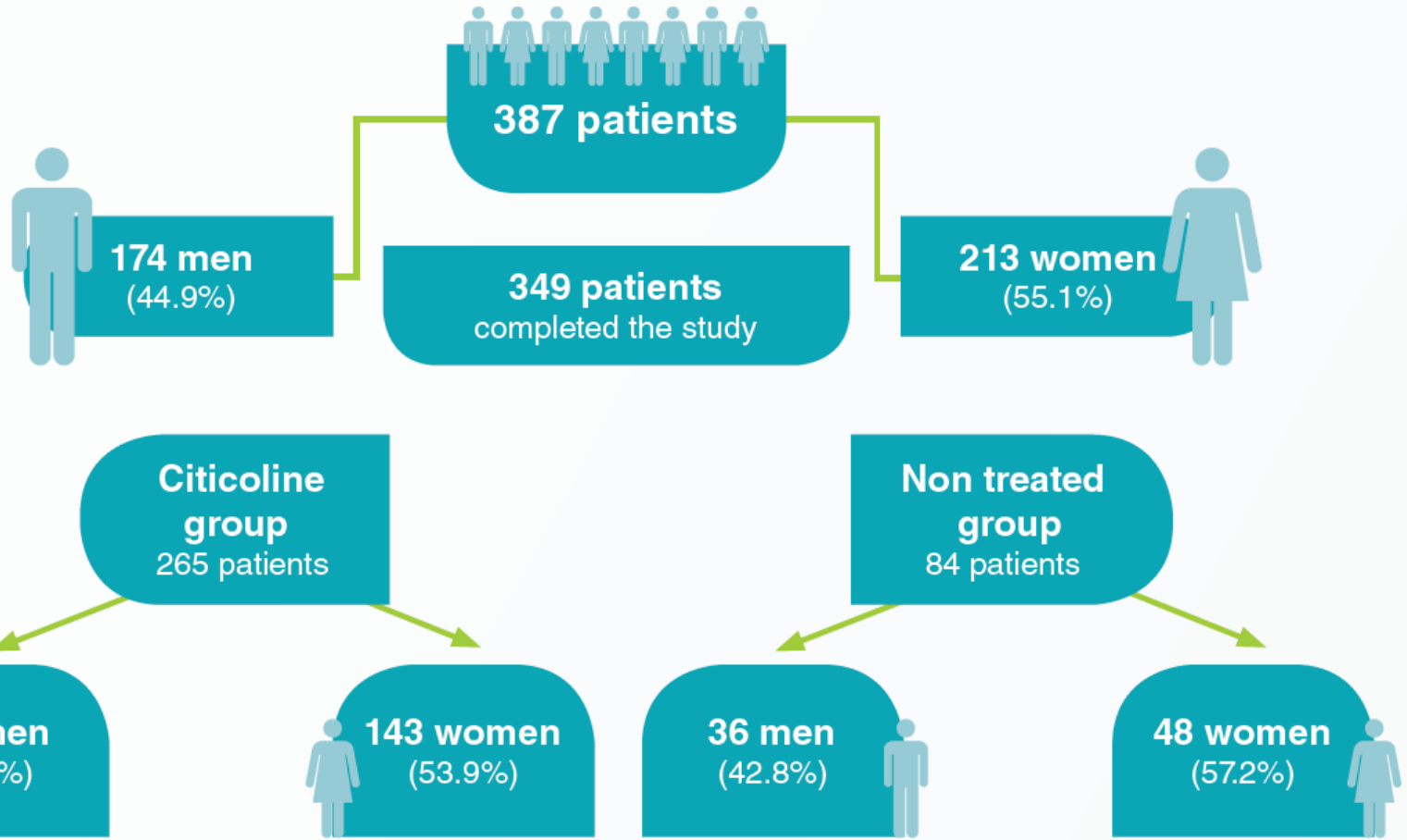
Razionale delle terapie di combinazione

- **Studi preclinici hanno chiaramente dimostrato che gli AChEIs + i precursori colinergici possono essere efficaci sia nella DA che nella demenza mista, poichè aumentano i livelli intrasinaptici di Ach più di quanto possano fare i singoli farmaci da soli (The ASCOMALVA Study, Amenta et al., 2012)**
- **Meccanismi patogenetici comuni sia nella DA che nella DV**
- **Deficit colinergici nella demenza vascolare e nel deterioramento cognitivo vascolare in generale**

Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study

Antonino Maria Cotroneo[1]
Alberto Castagna[2]
Salvatore Putignano[3]
Roberto Lacava[2]
Fausto Fantò[4]
Francesco Monteleone[5]
Filomena Rocca[2]
Alba Malara[6]
Pietro Gareri[2]

Cohort gender flow chart



Mean age 79.9 ± 7.8 years old
(range 65 – 94)

Mean age 78.9 ± 7.01 years old
(range 67 – 90)

Clinical Interventions in Aging 2013:8 131–137

Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study

Citicoline group	Non treated group	P
• 265 pts	• 84 pts	
• Mean age 79.9 ± 7.8 years old (range 65–94)	• Mean age 78.9 ± 7.01 years old (range 67–90)	ns
• 122 men (46.1%), 143 women (53.9%)	• 36 men (42.8%), 48 women (57.2%)	ns
• Education 6.1 ± 3.8 years	• Education 5.9 ± 2.6 years	ns
• Smokers (5.6%)	• Smokers (6.1%)	ns
• ADL 4.0 ± 1.8	• ADL 4.1 ± 1.6	ns
• IADL 5.6 ± 1.2	• IADL 5.7 ± 2.3	ns
• GDS 5.6 ± 2.2	• GDS 5.8 ± 1.4	ns
• CIRS 3.2 ± 1.3	• CIRS 3.4 ± 1.8	ns
• NPI 8.4 ± 4.5	• NPI 9.2 ± 2.1	ns
• Comorbidities	• Comorbidities	
– Hypertension (75%)	– Hypertension (77%)	ns
– Osteoarthritis (72%)	– Osteoarthritis (70%)	ns
– Heart disease (43%)	– Heart disease (38%)	ns
– Diabetes (35%)	– Diabetes (37%)	ns
– COPD (15%)	– COPD (18%)	ns
– Depression (20%)	– Depression (23%)	ns
– Stroke (15%)	– Stroke (11%)	ns
• Drugs	• Drugs	
– Cardiovascular drugs* (84%)	– Cardiovascular drugs* (81%)	ns
– NSAIDs** (48%)	– NSAIDs** (52%)	ns
– Antidiabetics (35%)	– Antidiabetics (37%)	ns
– Antidepressants (20%)	– Antidepressants (23%)	ns
– Others (20%)	– Others (24%)	ns

Notes: *Antihypertensive drugs, antiaggregants, diuretics, nitrates, β-blockers, digoxin; **Non-steroidal anti-inflammatory drugs.
Abbreviations: ADL, activities of daily living; CIRS, cumulative illness rating scale; COPD, chronic obstructive pulmonary disease; GDS, geriatric depression scale; IADL, instrumental activities of daily living; NPI, neuropsychiatric inventory scale; ns, non significant.

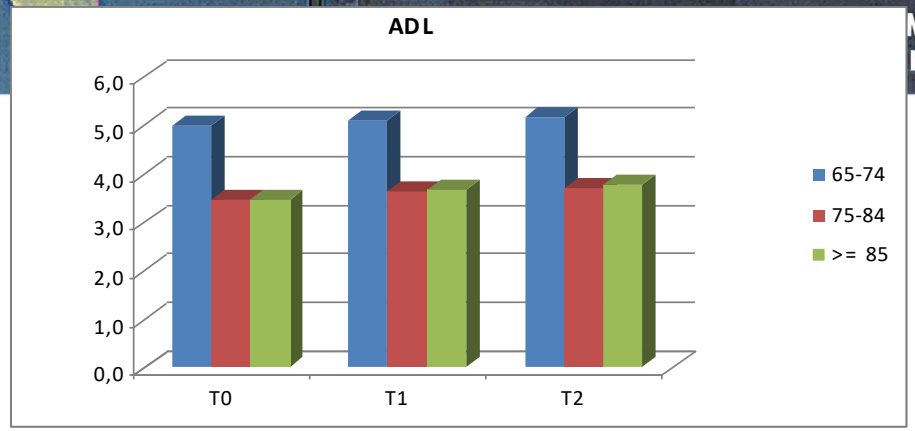
Clinical Interventions in Aging 2013:8 131–137

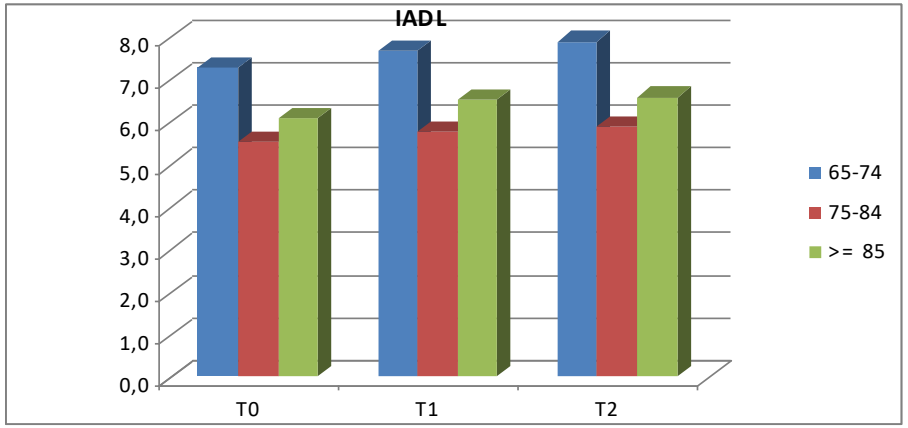
Years	T0	T1	T2
65-74	5,0	5,1	5,1
75-84	3,4	3,6	3,7
>= 85	3,5	3,6	3,8

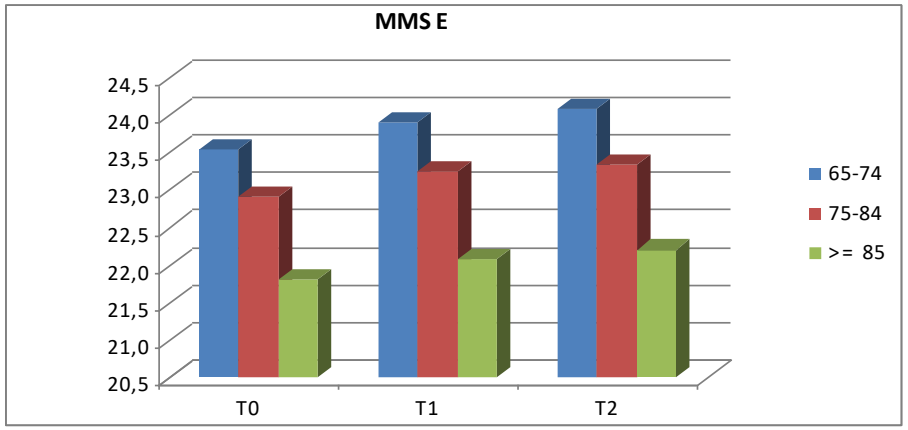
Years	T0	T1	T2
65-74	7,3	7,7	7,9
75-84	5,5	5,8	5,9
>= 85	6,1	6,6	6,6

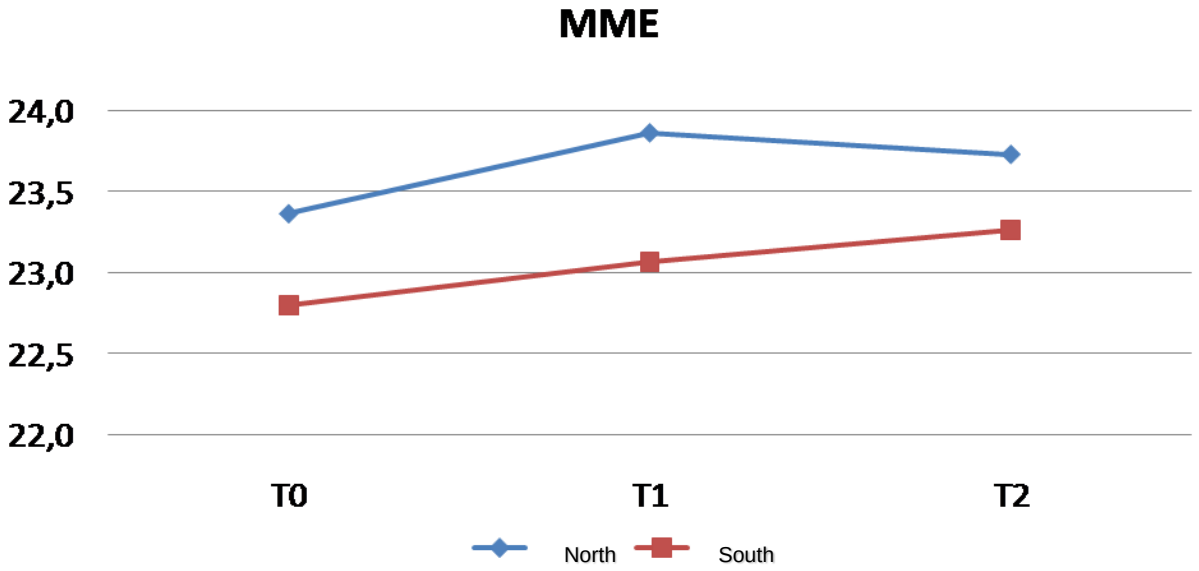
Years	T0	T1	T2
65-74	23,5	23,9	24,1
75-84	22,9	23,3	23,3
>= 85	21,8	22,1	22,2

p: 0,1642

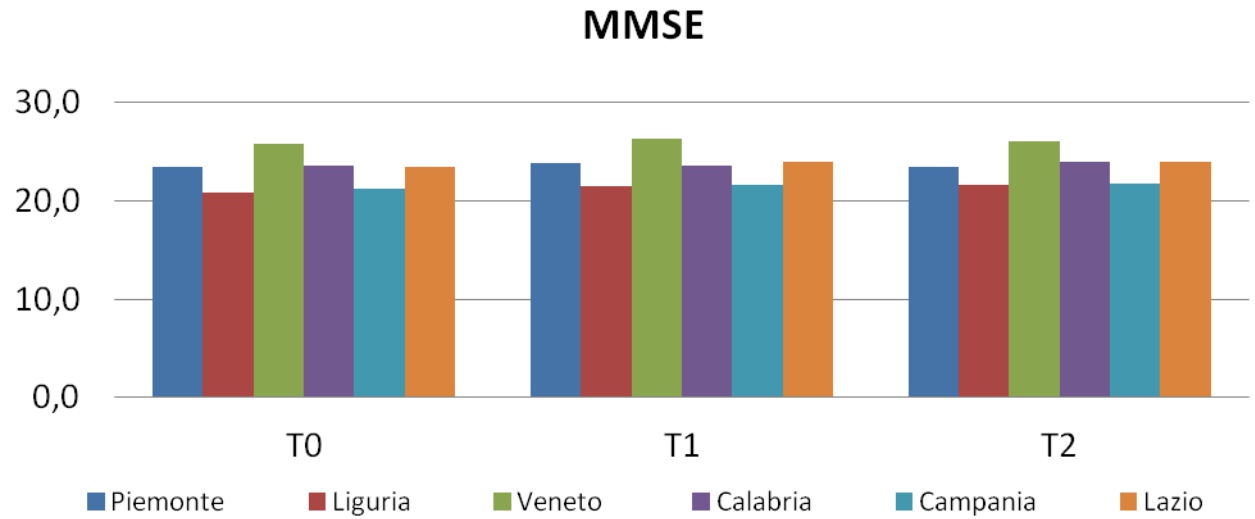




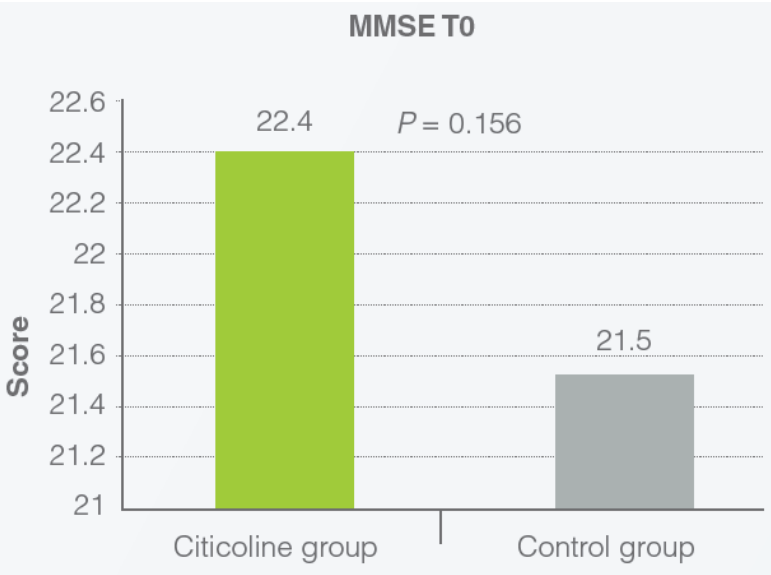


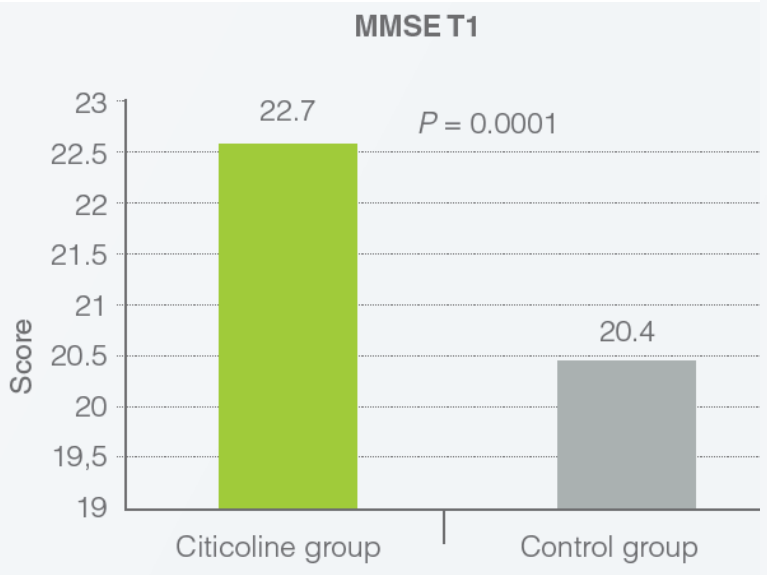


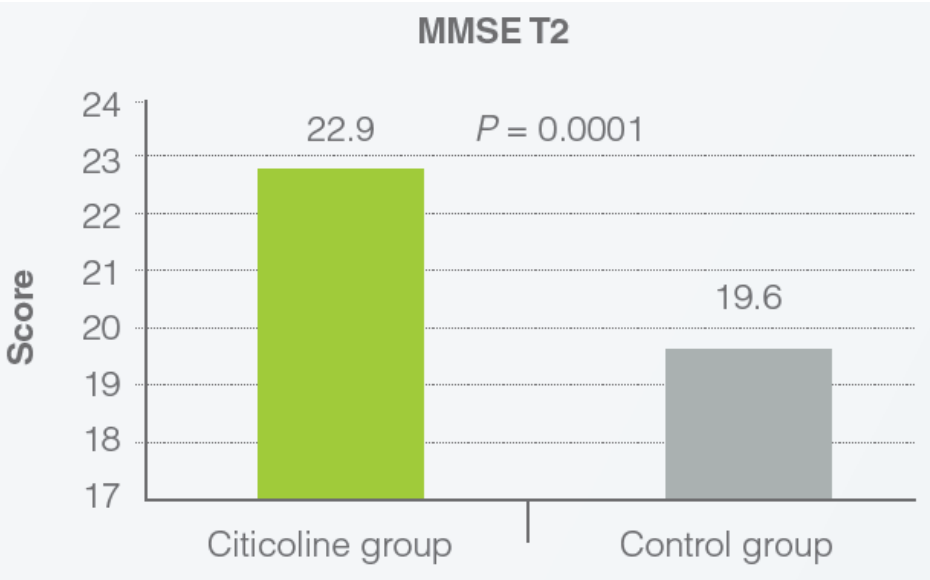
North	23,4	23,9	23,7
South	22,8	23,1	23,3



Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study







	MMSE Citicoline group		MMSE controls	
	T0-T1	T0-T2	T0-T1	T0-T2
t	0.863	1.439	1	1.792
P	0.388	0.151	0.319	0.075

Clinical Interventions in Aging 2013:8 131–137

Effectiveness and safety of citicoline in mild vascular cognitive impairment: the IDEALE study

Conclusions

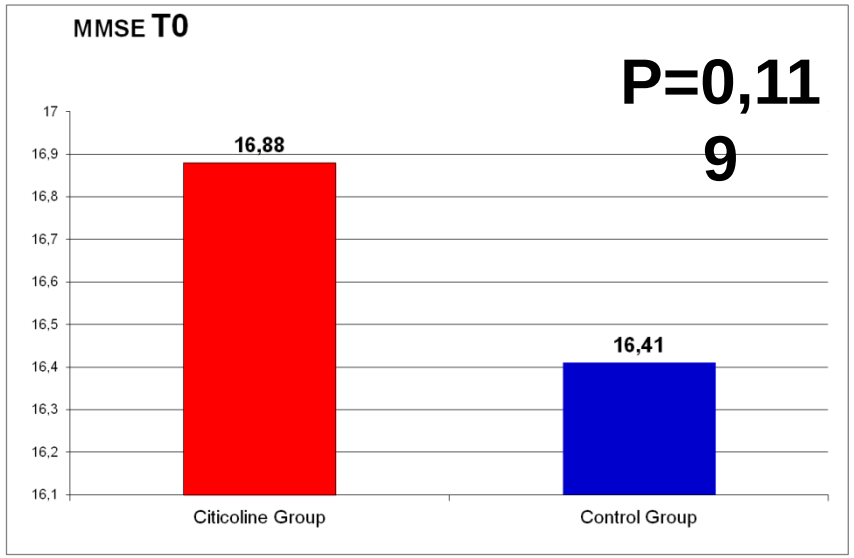
- An improvement of MMSE score was found between T2, T1 and T0 (increase of 0.5 points)
- The untreated group showed a decline in MMSE score (-1.9 points); significant difference among the treated and untreated groups
- ADL and IADL scores remained substantially unchanged in both groups
- A slight difference was found in GDS score among the study and control groups (p=0.06, ns).
- **No adverse events** were recorded over the course of the study.

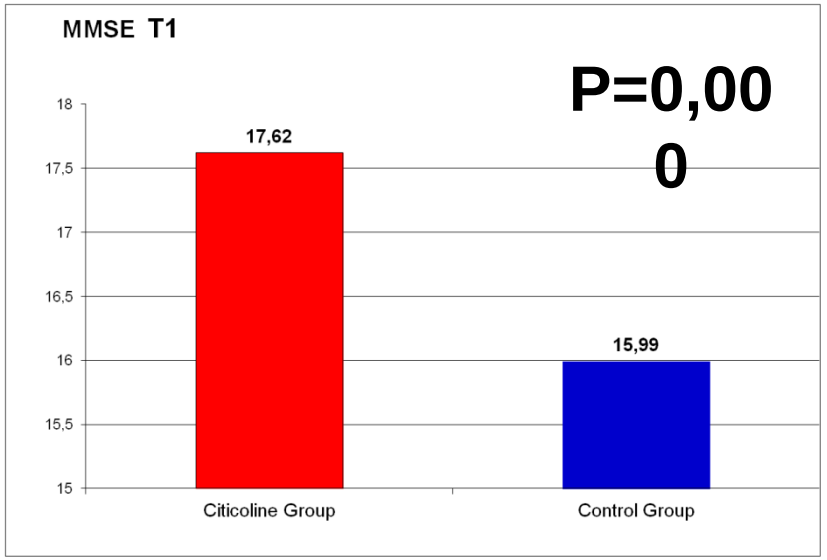
- **This study showed that citicoline is effective and safe, therefore it can be recommended in mild vascular cognitive impairment.**

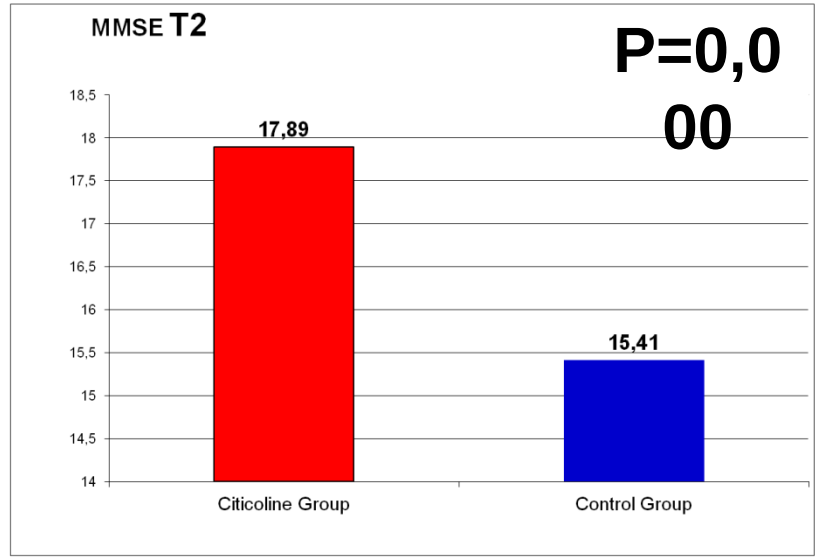
Clinical Interventions in Aging 2013:8 131–137

The Citicholinage Study: Citicoline Plus Cholinesterase Inhibitors in Aged Patients Affected with Alzheimer's Disease Study

MMSE at Baseline, T1 and T2



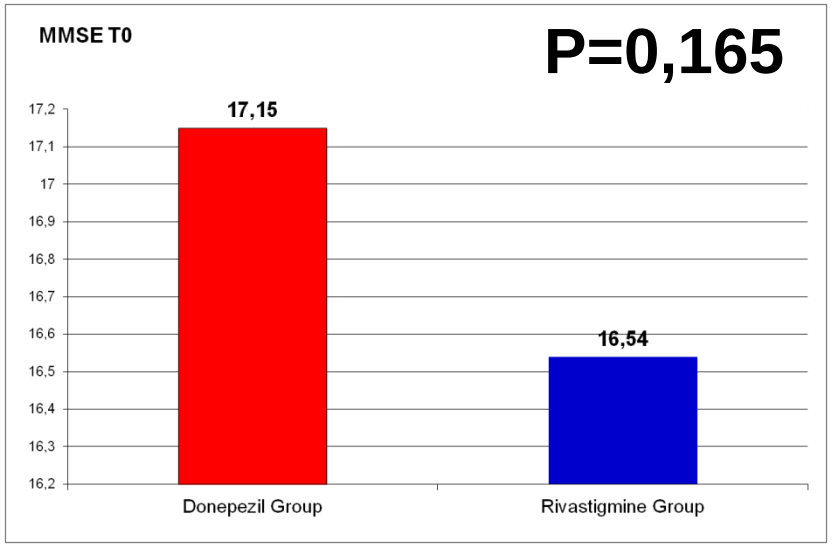


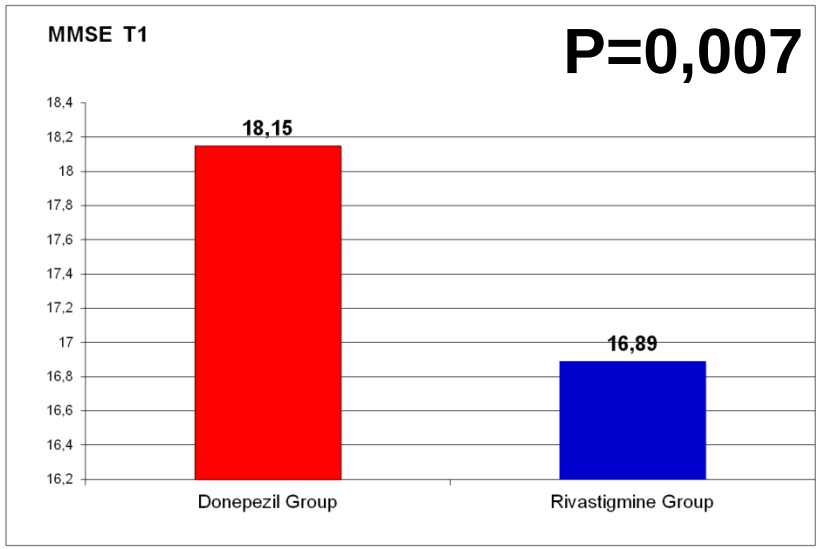


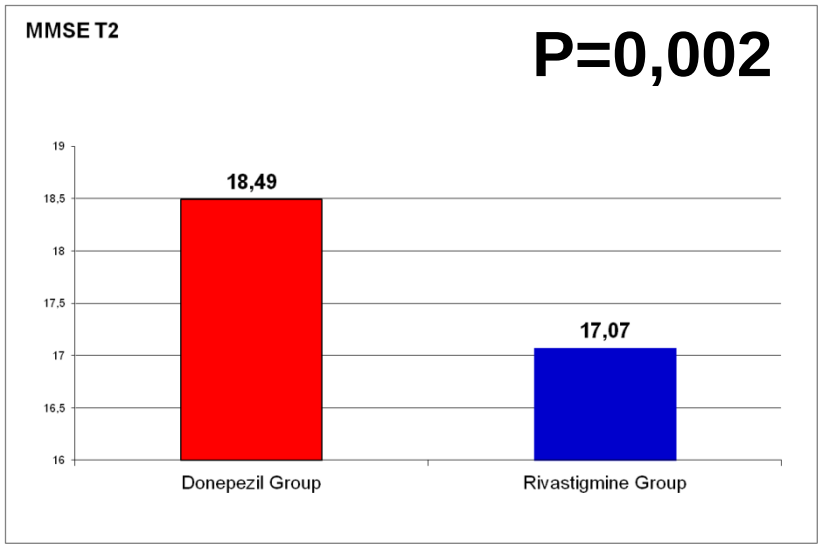
Journal of Alzheimer's Disease 56 (2017) 557–565

The Citicholinage Study: Citicoline Plus Cholinesterase Inhibitors in Aged Patients Affected with Alzheimer's Disease Study

MMSE scores over time in the groups donezepil+citicoline (n=144) and rivastigmine + citicoline (n=105)







Journal of Alzheimer's Disease 56 (2017) 557–565

Key Points

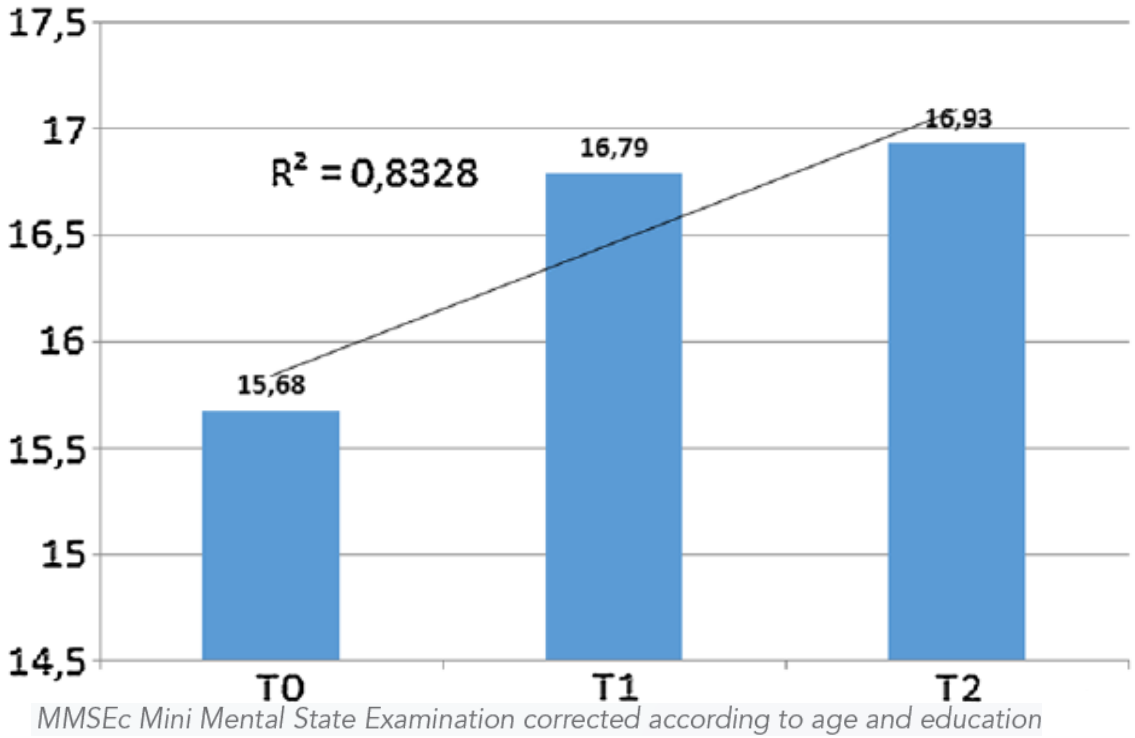
The CITIRIVAD study was a retrospective case-control study.

It was performed on 174 consecutive outpatients aged 65 years old or older, affected with AD or MD, treated with rivastigmine patches + citicoline 1000 mg/day given orally (group A) or with rivastigmine alone (group B).

Data showed the effectiveness of combined administration (citicoline + rivastigmine) versus the AchEI alone, mainly in slowing disease progression.

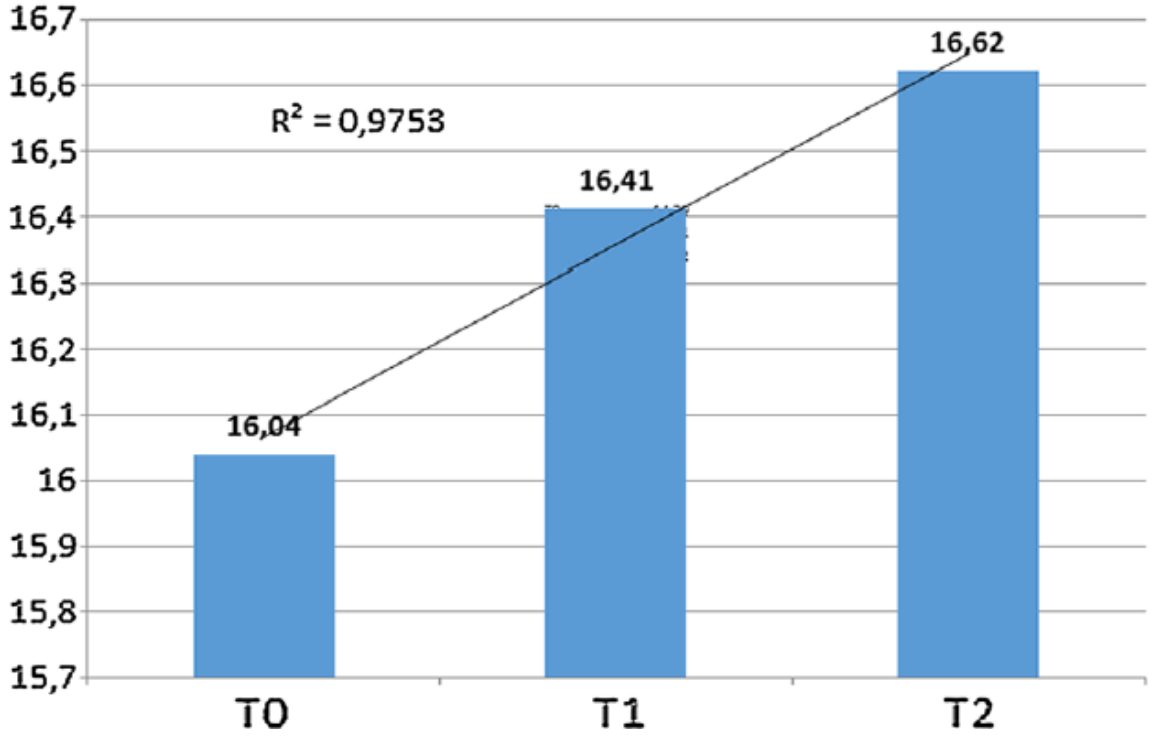
Mean MMSEc score

Alzheimer's disease



MMSEc Mini Mental State Examination corrected according to age and education

Mixed dementia



The CITIRIVAD Study: CITIcoline plus RIVAstigmine in Elderly Patients Affected with Dementia Study

Cotroneo A.M. et al Clin Drug Investig. 2016 Dec;36(12):1059-1065

Name of the study	Type of study	Patients (n) and kind of dementia	Combination therapy	Baseline (MMSE score) Cases vs controls	3 months (MMSE score) Cases vs controls	6 months (MMSE score) Cases vs controls	9 months (MMSE score) Cases vs controls	12 months (MMSE score) Cases vs controls
CITIRIVAD	Retrospective Multi-centric Case-control	n = 174 AD; MD	Citicoline 1g + rivastigmine	16.04±3.13 14.79±2.75	**16.41±3.26*** **14.33±2.96** **p=0.001**	// //	**16.62±3.55*** **13.2±2.62** **p=0.000**	// //
CITICHOLINAGE	Retrospective Multi-centric Case-control	n = 448 AD	Citicoline 1g + AchEIs	16.88±3.38 16.41±2.97	**17.62±3.64*** **15.99±3.16** **p=0.000**	// //	**17.89±3.54*** **15.41±3.16** **p=0.000**	// //
CITIMEM	Retrospective Multi-centric Case-control	n = 126 AD; MD	Citicoline 1g + memantine	16.6 ± 2.9 16.6±2.9	// //	**17.4 ± 2.7*** **15.6±2.9** **p=0.003**	// //	**17.7 ± 2.8*** **14.6±3** **p=0.000**
CITIMERIVA	Retrospective Multi-centric Case-control	n = 104 AD	Citicoline 1g + memantine + rivastigmine	13.63 ± 2.46 14.25 ± 2.66	// //	**14.17 ± 2.24*** 14.24 ± 2.88 **T0vsT1 p=0.008**	// //	**14.32 ± 2.53*** 14.00 ± 2.97 **T0vsT2 p=0.002**
CITIMEA	Retrospective Multi-centric Case-control	n = 170 AD	Citicoline 1g + memantine + AchEIs	14.88 ± 2.95 14.37 ± 2.63	// //	14.95 ± 2.63 14.19 ± 2.81	// //	**15.09 ± 3.00*** **14.03 ± 2.92** **p=0.024**
CITIDEMAGE	Retrospective Multi-centric Case-control	n = 169 AD	Citicoline 1g + AchEIs + memantine	15.85 ± 2.86 15.11 ± 3	// //	**16.39 ± 2.93*** **14.95 ± 3.23** **p=0.003**	// //	**16.43±3.08*** **15.12±3.52** **p=0.011**

Il presente

- **Ottimizzare le terapie che possano in qualche modo rallentare la progressione della malattia**

- **Approccio colinergico associando un precursore come colina alfoscerato o citicolina può attualmente essere una valida alternativa per cercare di ritardare la progressione del declino cognitivo nell'AD e nella MD**

Il futuro….

- **Ricercare molecole con evidenza di efficacia e tollerabilità….**
- **Anticorpi monoclonali?**
- **Mitocondri?**
- **Altro?**