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SOCIETÀ ITALIANA  
DI GERONTOLOGIA  
E GERIATRIA

*Citicolina: un tassello nel puzzle del  
paziente ansioso complesso con deficit  
cognitivo e disordini comportamentali*

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**15-20%** Demenza a Corpi di Lewy, Demenza Fronto-Temporale, Altre

**15-20%** Demenza vascolare e mis

**>60%** Demenza di Alzheimer

**Cambiamenti biologici legati all'età che contribuiscono alla neurodegenerazione nelle demenze più comuni**



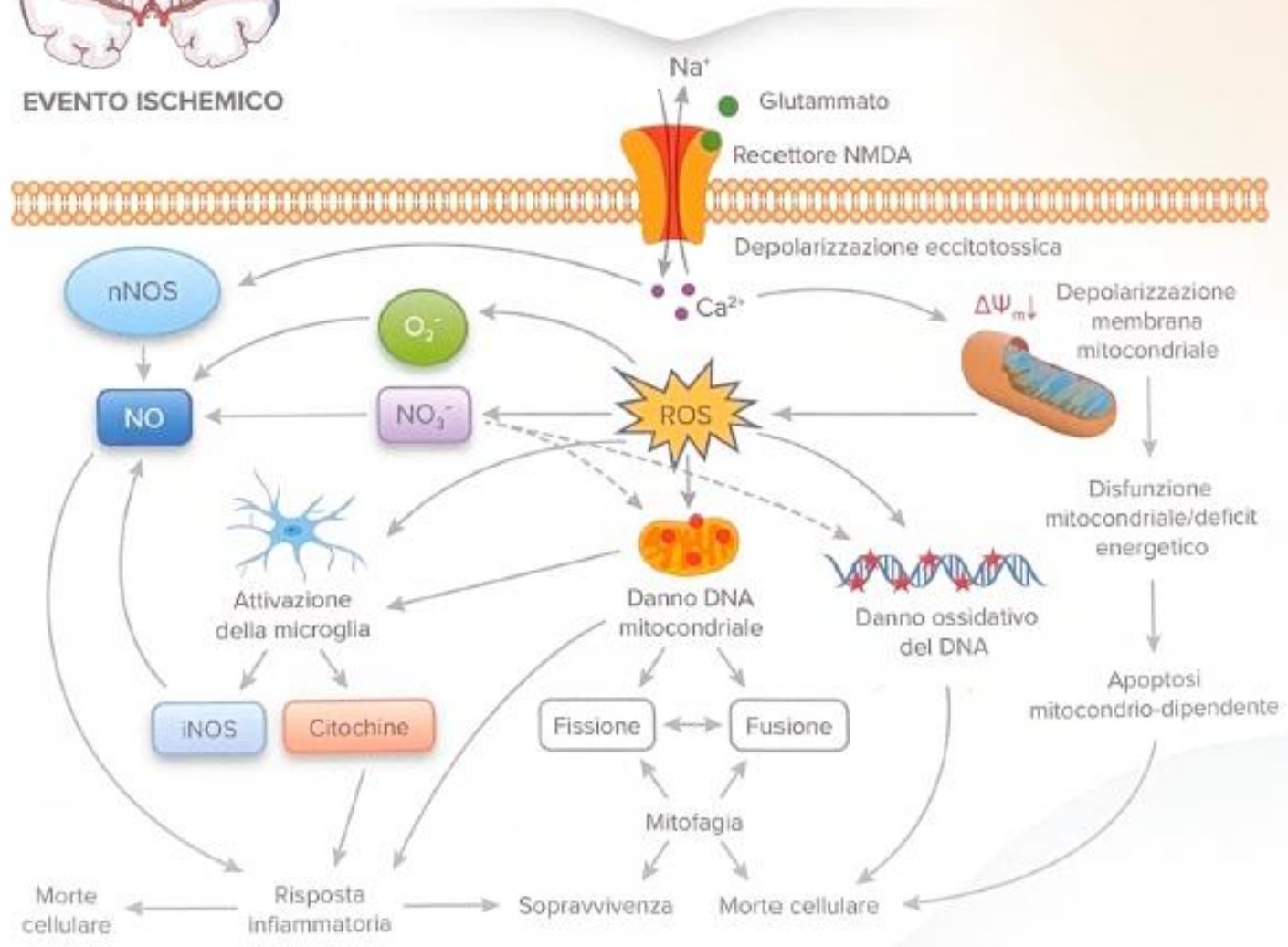
**Pathway patologici nella cascata ischemica cerebrale che coinvolgono la funzione mitocondriale e la generazione di ROS<sup>8</sup>**



**EVENTO ISCHEMICO**

Flusso sanguigno ↓  
 Apporto di ossigeno e nutrienti ↓  
 Produzione di ATP ↓

Eccitotossicità da glutammato



**DEGENERAZIONE SINAPTICA**

**DANNO E MORTE NEURONALE**

**DECLINO COGNITIVO**

# Key points

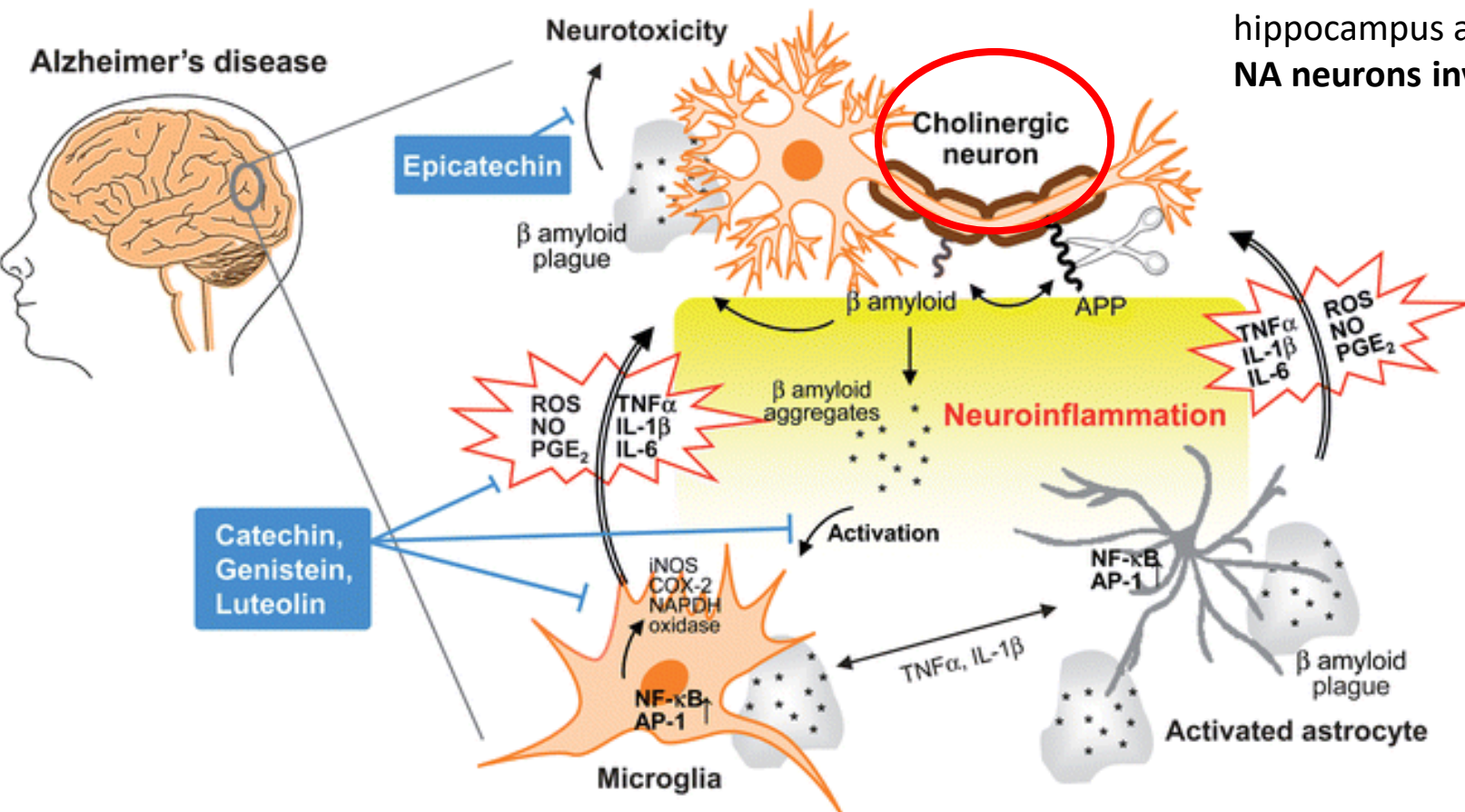
- Citicoline: an old drug with new perspectives
- Citicoline in cognitive impairment. What do we have learned from previous studies
- Combination therapies: evidence from literature
- What can we expect from future studies and why?

# The final target: the cholinergic neuron

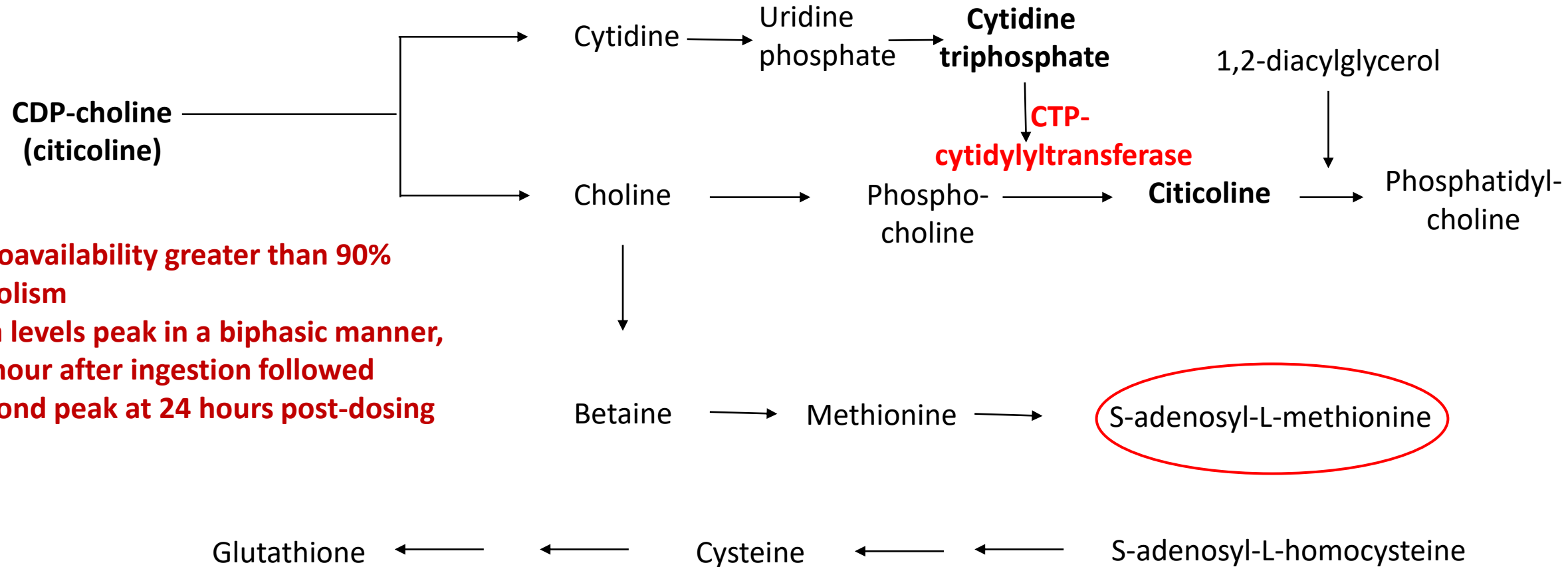
In particular cholinergic neurons and pathways...

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

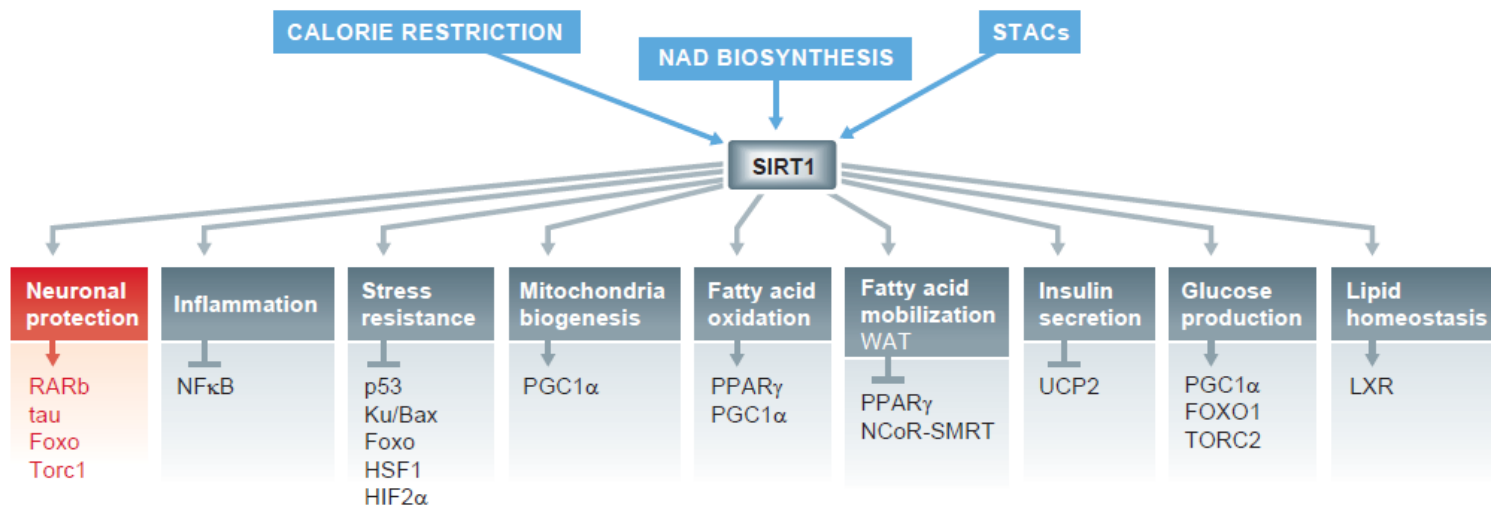


The mechanism by which Ab induces inflammation and cell death is unclear but may involve a complex cascade of biochemical events resulting in the imbalance of intracellular ions, production of inflammatory mediators and free radicals, and finally, apoptotic cell death that culminates in massive atrophy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



- 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

Adibhatla et al., Stroke, 2001, modif.



EMBO Mol Med (2013) 5, 344–352

**Figure 1. The targets and interacting partners of SIRT1.** SIRT1 has many targets that play roles in different molecular pathways including neuronal protection, inflammation, stress resistance, mitochondrial biogenesis, fatty acid oxidation and mobilization, insulin secretion, glucose production and lipid homeostasis. SIRT1 is activated by CR, NAD biosynthesis and small molecule sirtuin activators (STACs).

### Protective effects and mechanisms of sirtuins in the nervous system

Feng Zhang<sup>a,c,\*</sup>, Suping Wang<sup>a,c,\*</sup>, Li Gan<sup>b</sup>, Peter S. Vosler<sup>c</sup>, Yanqin Gao<sup>a,c</sup>, and Jun Chen<sup>a,c,d</sup>

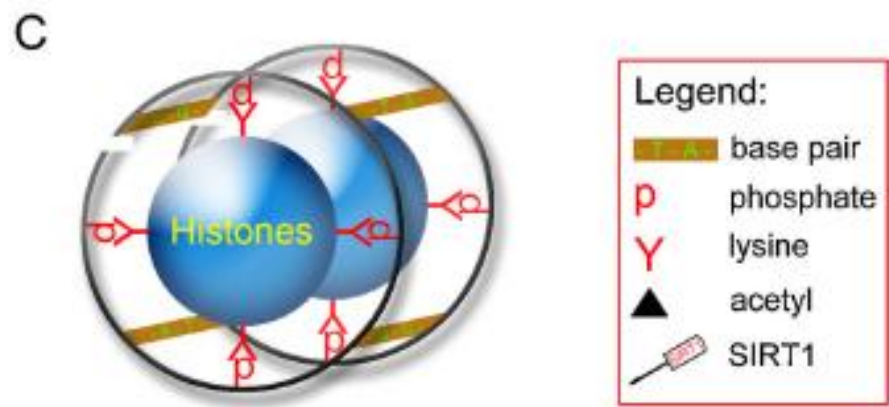
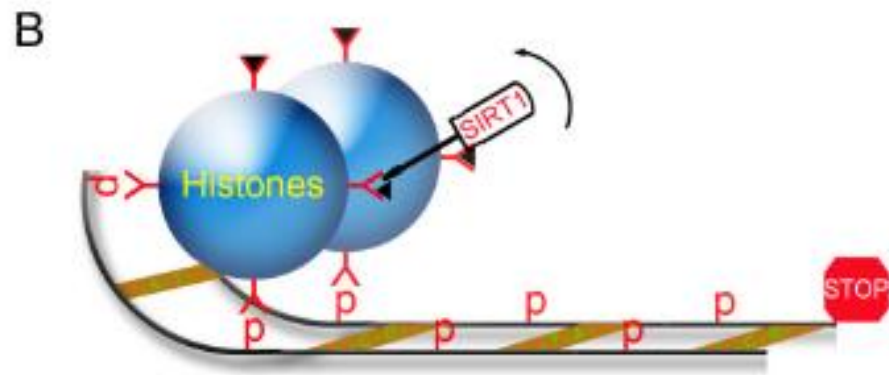
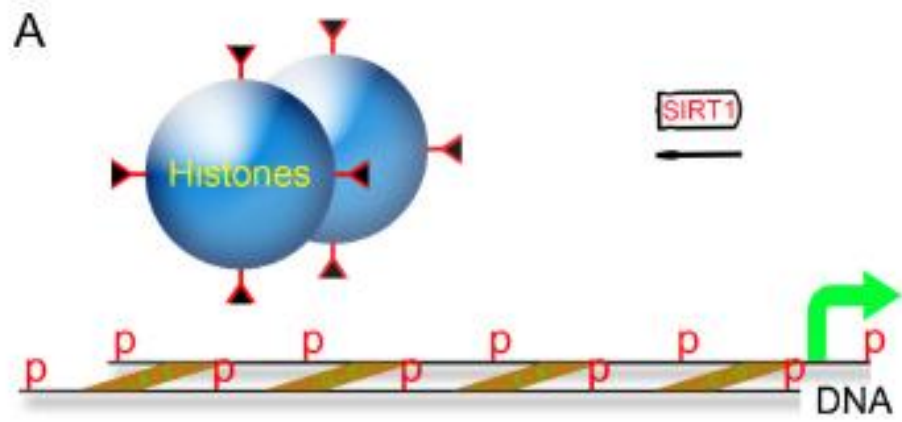
*Prog Neurobiol.* 2011 November ; 95(3): 373–395.

- Sirtuins are NAD<sup>+</sup>-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.

AD  
PD  
Prion disease  
ALS

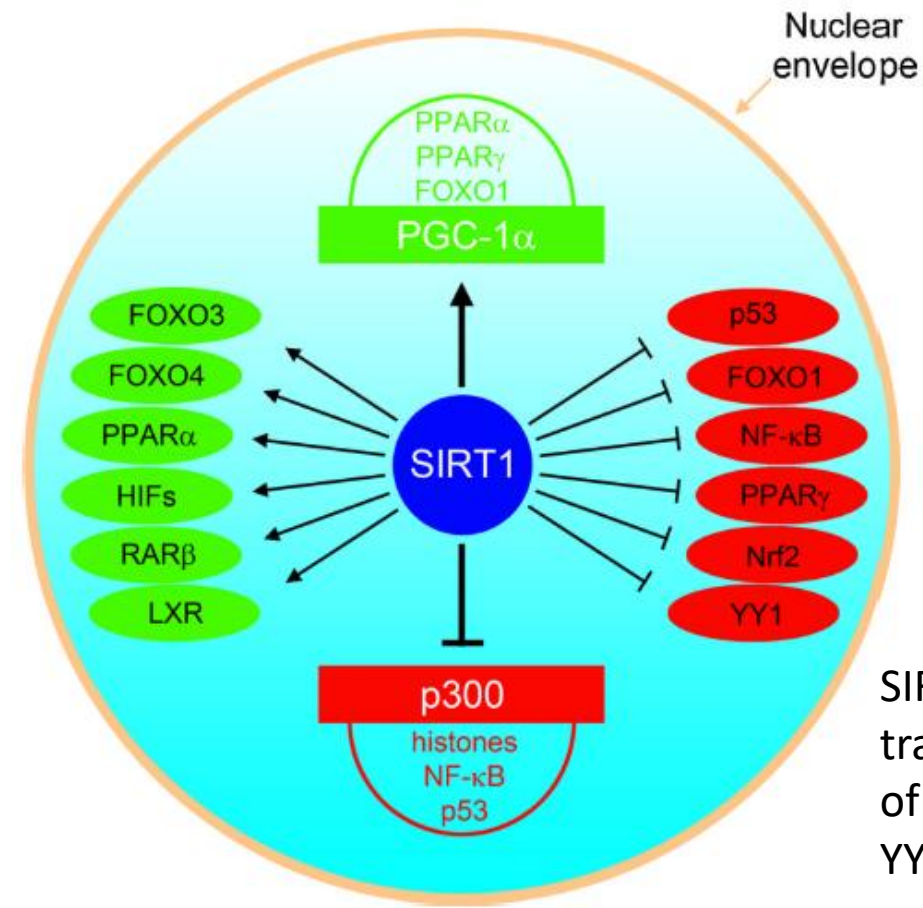
HD  
MS  
Cerebral ischemia

**Protective effects in:** ALS



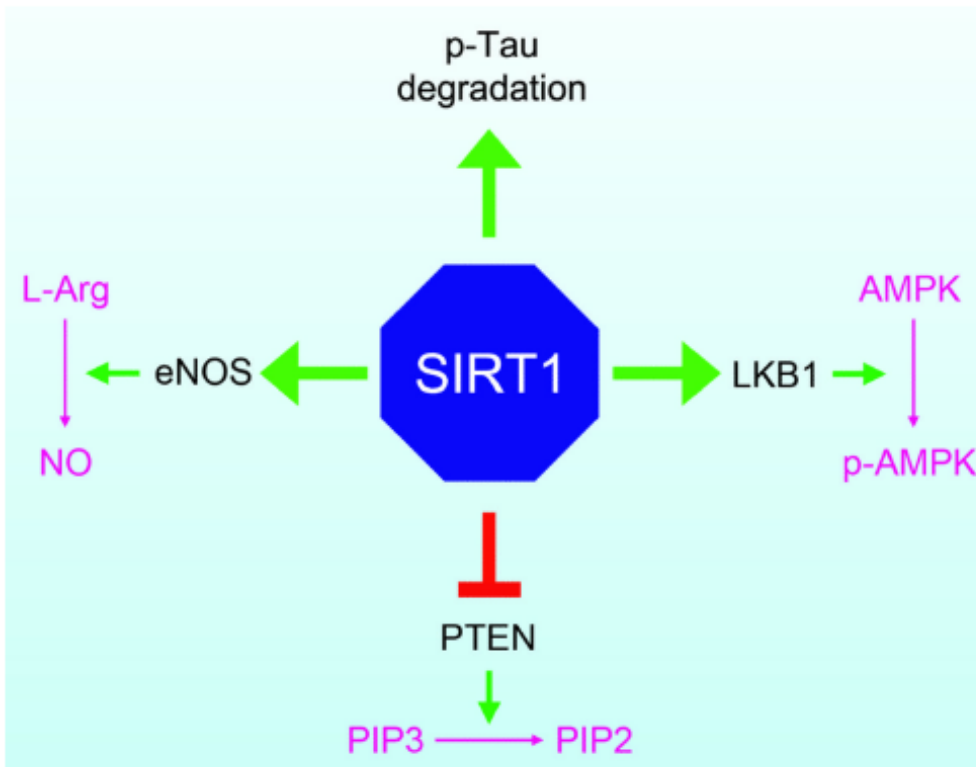
**Legend:**

- base pair
- p** phosphate
- Y** lysine
- acetyl
- SIRT1



SIRT 1 decreases transcriptional activity of p53, NF- $\kappa$ B, FOXO1, YY1, Nrf2 and PPAR $\gamma$ .

**Figure 3. SIRT1 globally silences gene transcription by deacetylating histones**  
 (a) When SIRT1 is not active, the histones are acetylated and unable to bind DNA, thus facilitating gene transcription. (b) Once activated, SIRT1 deacetylates histones, giving them a net positive charge. Histones are then free to bind DNA at phosphate moieties and interfere with gene transcription. (c) Once histones have fully gained their positive charge upon complete deacetylation of histone lysines, DNA winds around the histones, making gene transcription unavailable and leading to genome-wide gene silencing.



**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.

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

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

# Safety

- Low level of toxicological concern; administration of choline with cytidine in the form of CDP-choline lowers the toxicity index an additional 20 fold
- Occasional digestive intolerance and occasional excitability or restlessness in the first days of treatment (especially parenterally)
- Self-limiting headache, tingling sensation, numbness
- No clinically significant ECG and EEG abnormalities

Gareri et al., 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**

La tabella 1 riassume le azioni pleiotropiche della citicolina.

La Citicolina:
● è efficace nel deterioramento cognitivo di diversa eziologia, demenza di Alzheimer, demenza mista, Parkinson demenza, demenza vascolare, deterioramento cognitivo vascolare, glaucoma, ambliopia, trauma cranico <sup>7-9</sup>
● migliora il richiamo immediato e tardivo di parole, oggetti, la memoria verbale ed a lungo termine <sup>10</sup>
● aumenta la sintesi di fosfatidilcolina, fosfatidiletanolamina e fosfatidilserina <sup>11</sup>
● aumenta la sintesi di acetilcolina <sup>11</sup>
● previene l'accumulo di acidi grassi liberi e la generazione di radicali liberi al sito di ischemia <sup>11</sup>
● inibisce l'apoptosi associata ad ischemia cerebrale prevenendo l'attivazione della caspasi-3 <sup>7</sup>
● migliora il metabolismo energetico mitocondriale prevenendo la perdita di cardiolipina <sup>7,11,12</sup>
● aumenta il metabolismo cerebrale ed i livelli di noradrenalina e dopamina nel Sistema Nervoso Centrale (SNC) <sup>8,13</sup>
● promuove effetti neuroprotettivi in condizioni di ipossia ed ischemia, migliora apprendimento e memoria in modelli animali di invecchiamento cerebrale e ripristina l'attività dell'ATPasi mitocondriale e dell'ATPasi di membrana Na <sup>+</sup> /K <sup>+</sup> <sup>9,13</sup>
● inibisce l'attivazione della fosfolipasi A <sub>2</sub> ed accelera il riassorbimento dell'edema cerebrale in vari modelli sperimentali <sup>9,13</sup>
● riduce/ritarda l'efflusso neuronale di glutammato, stimola la sintesi di glutazione e promuove neurogenesi, sinaptogenesi e gliagenesi <sup>14-19</sup>
● aumenta l'espressione della SIRT1 nel cervello di ratto, nelle colture neuronali e nelle cellule mononucleate sieriche circolanti <sup>17</sup>
● aumenta l'attività dei livelli sierici di acetilcolinesterasi (AChE), butirrilcolinesterasi (BChE) e neprilisina (NEP) <sup>20,21</sup>

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The CITIMEM study: A pilot study. Optimizing pharmacological treatment in dementia

Pietro Gareri<sup>a,\*</sup>, Antonino Maria Cotroneo<sup>b</sup>, Giuseppe Orsitto<sup>c</sup>, Salvatore Putignano<sup>d</sup>



## Latin American Delphi Consensus on Vascular Cognitive Impairment: Definitions, Clinical Features, Pathophysiology, Prevention and Treatment

Alberto J Mimenza Alvarado<sup>1\*</sup>, Carlos G Cantú Brito<sup>2</sup>, Gustavo C Roman<sup>3</sup>, Pietro Gareri<sup>4</sup>, Sara G Aguilar Navarro<sup>1</sup>, Jose L Ruiz Sandoval<sup>5</sup>, Juan M Calleja Castillo<sup>6</sup>, Carolina Velazquez<sup>7</sup>, Gustavo Pradilla Ardila<sup>8</sup>, María S Caceres Merino<sup>9</sup>, Juan C Duran Quiroz<sup>10</sup>, Nilton C Capuñay<sup>11</sup>, Ciro Gaona<sup>12</sup>, Jose S Ramirez<sup>13</sup>, Carlos Arteaga Vasquez<sup>14</sup>, Hector Franco<sup>15</sup>, Felipe Villareal<sup>16</sup>, Hector Orrego Castellanos<sup>17</sup>, Xinia M Jiménez Campos<sup>18</sup> and Julio J Secades<sup>19</sup>

**1. Note there is a cognitive deficit**

Reference or complaint by the patient, his/her family or health personnel.  
The "deterioration" may be inferred.



**2. Make objective the significant cognitive impairment**

Comparison to performance standard.



**3. Determine the impact of cognitive deficit on daily life**

Need for support to perform independent previous activities.



**4. Determine that cause is certainly vascular**

Medical history, physical examination, neuroimaging.



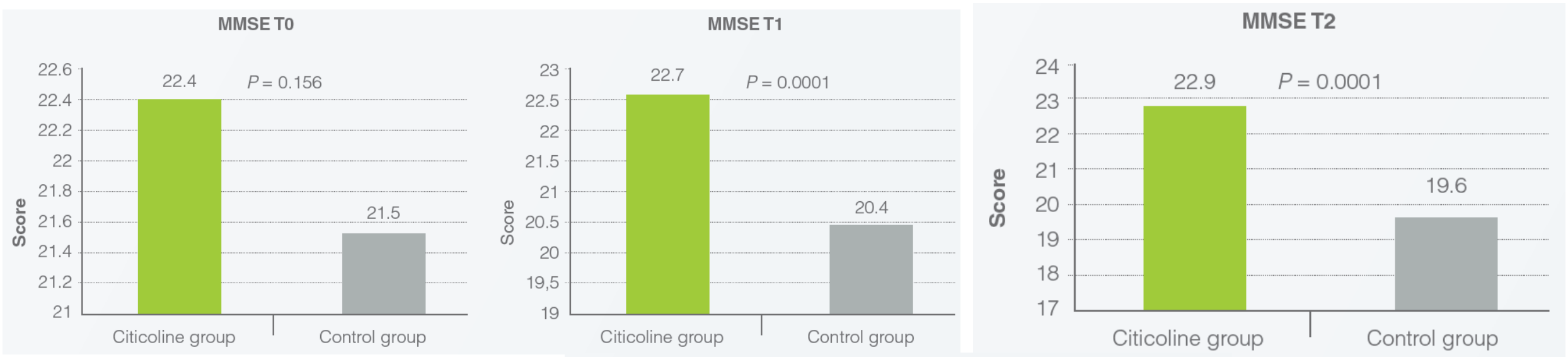
**5. Rule out other causes and determine cognitive comorbidity**

Clinical history, physical examination, neuroimaging, biomarkers.

**Figure 1** Diagnostic algorithm for vascular cognitive impairment.

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

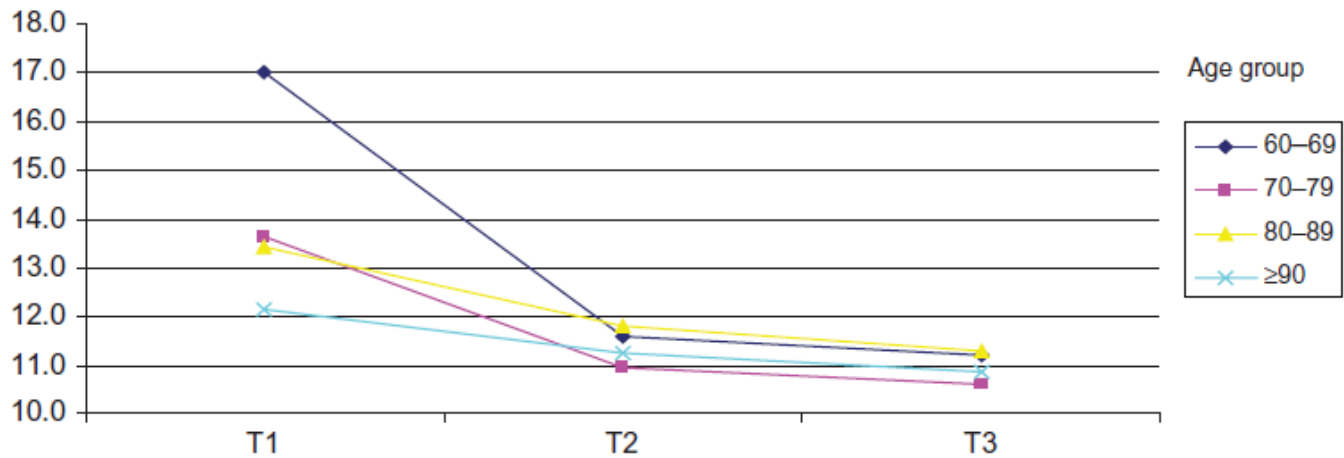
Clinical Interventions in Aging 2013:8 | 131–137



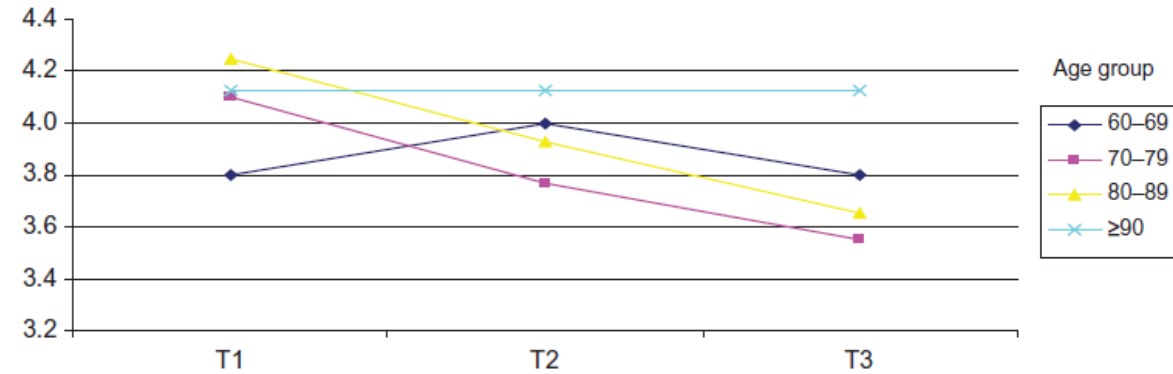
Antonino Maria Cotroneo<sup>1</sup>  
 Alberto Castagna<sup>2</sup>  
 Salvatore Putignano<sup>3</sup>  
 Roberto Lacava<sup>2</sup>  
 Fausto Fantò<sup>4</sup>  
 Francesco Monteleone<sup>5</sup>  
 Filomena Rocca<sup>2</sup>  
 Alba Malara<sup>6</sup>  
 Pietro Gareri<sup>2</sup>

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

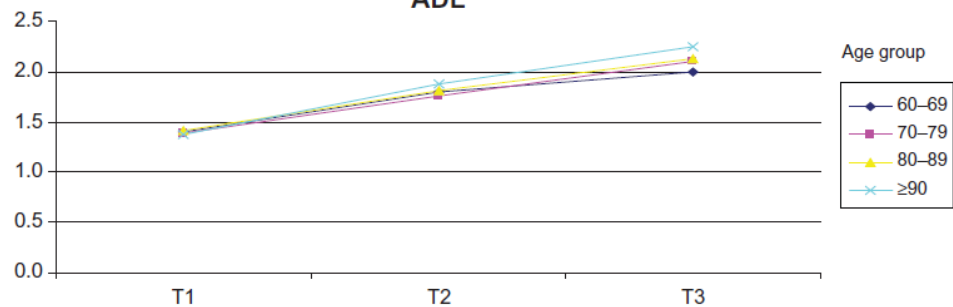
NIHSS



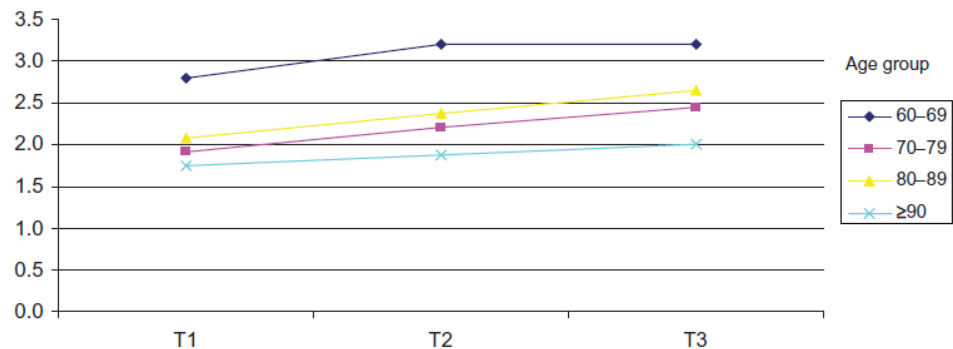
RANKIN



ADL



IADL



- In sub-acute ischemic cerebrovascular disease, administration of citicoline at the intravenous dose of 2000 mg in 500 cc of saline for 5 days or 10 days has proven to be effective in improving functional independence and in reducing the burden of care.

- After 5 days (80% of cases), or 10 days (20% of cases; T2), or 2 months (T3) since the beginning of treatment, there was an improvement in key measures of performance. This was more evident in the younger old-age groups.

- No major side effects in any phase of the study

- Phospholipids (PC, PE, PS)
- Neurotransmitters (Ach, DA, NA)
- Neuroprotective and oxidative stress (sirtuin-1, glutathione synthesis)
- Mitochondrial dysfunction (cardiolipin)
- Glutamate
- Synaptogenesis, gliogenesis

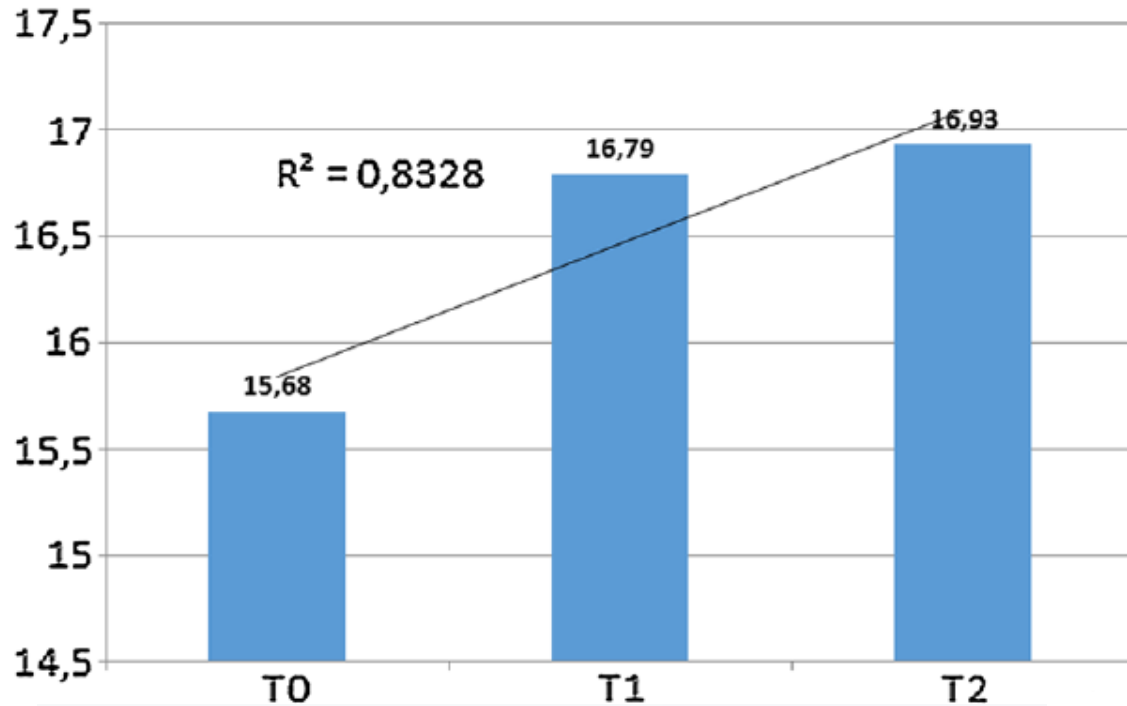
**•THE CITIDEMAGE  
Study**

- The CITIMEM Study
- 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 some previous studies

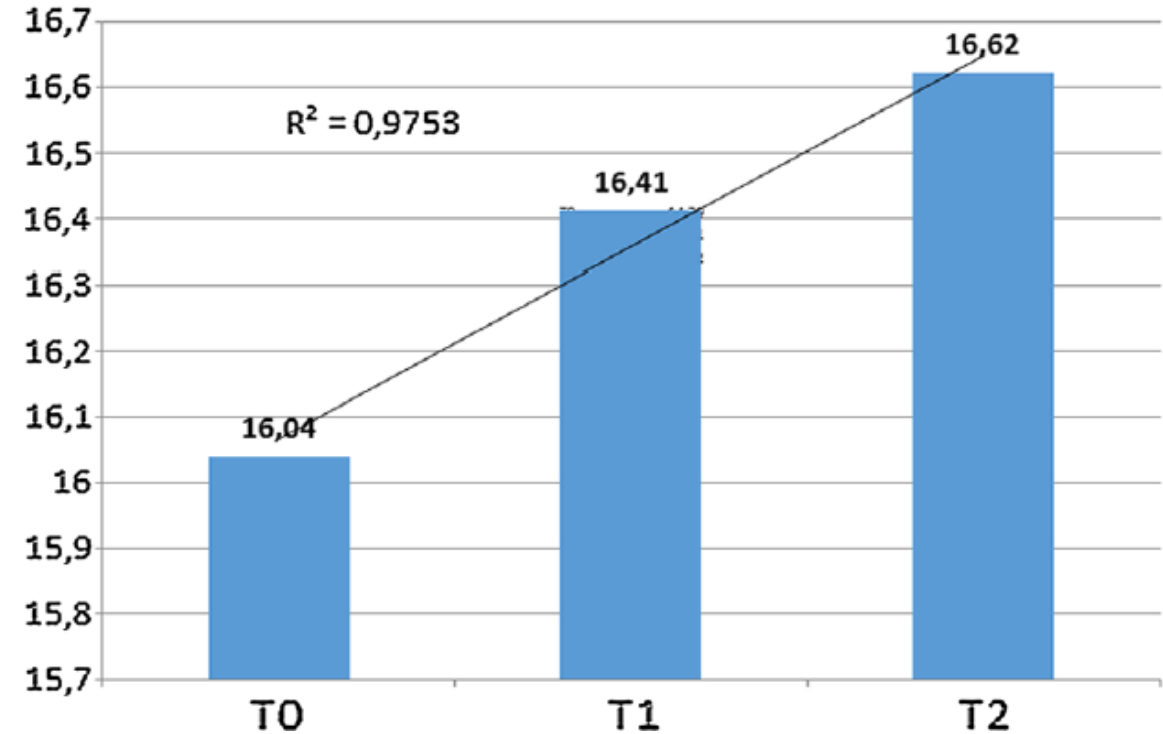
# Mean MMSEc score

## Alzheimer's disease



MMSEc Mini Mental State Examination corrected according to age and education

## Mixed dementia



Clin Drug Investig. 2016 Dec;36(12):1059-1065

### 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.

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

MMSEc	Cases		Controls		p value (ANOVA)
	AD	MD	AD	MD	
	rivastigmine +citicoline 1G		rivastigmine		
	n = 62	n = 30	n = 53	n = 29	
	Alzheimer's disease	Mixed dementia	Alzheimer's disease	Mixed dementia	
T0	15.68 ± 3.03	16.04 ± 3.13	15.32 ± 3.55	14.79 ± 2.75	0.447
T1	16.79 ± 2.84	16.41 ± 3.26	14.81 ± 3.58	14.33 ± 2.96	0.001
T2	16.93 ± 3.00	16.62 ± 3.55	13.97 ± 3.56	13.20 ± 2.62	0.000

MMSEc Mini Mental State Examination corrected according to age and education, CT combined treatment, rivastigmine + citicoline, AD Alzheimer's disease, MD mixed dementia.

# AD

## Alzheimer's disease

CT: rivastigmine +citicoline 1G

Controls rivastigmine

MMSE <sub>c</sub>	Cases (CT), n = 62	Controls (rivastigmine), n = 53	p value
T0	15.68 ± 3.03	15.32 ± 3.55	0.565
T1	16.79 ± 2.84	14.81 ± 3.58	0.001
T2	16.93 ± 3.00	13.97 ± 3.56	0.000

# MD

## Mixed Dementia

CT: rivastigmine +citicoline 1G

Controls rivastigmine

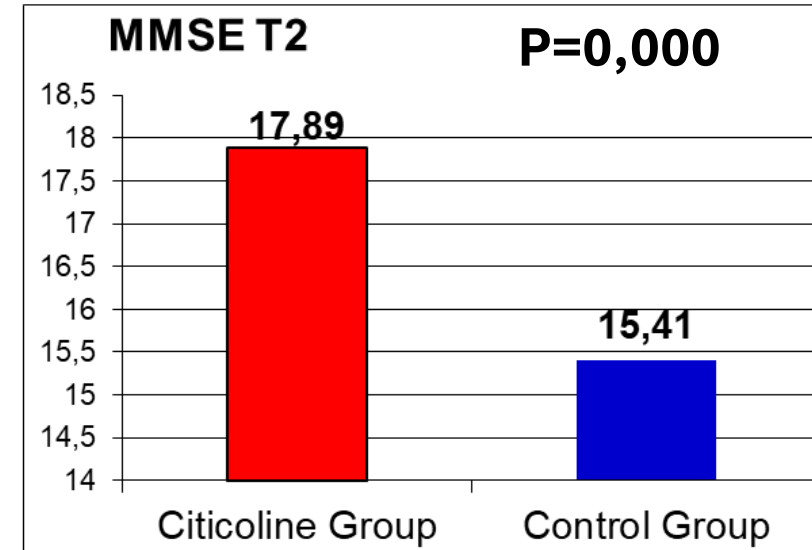
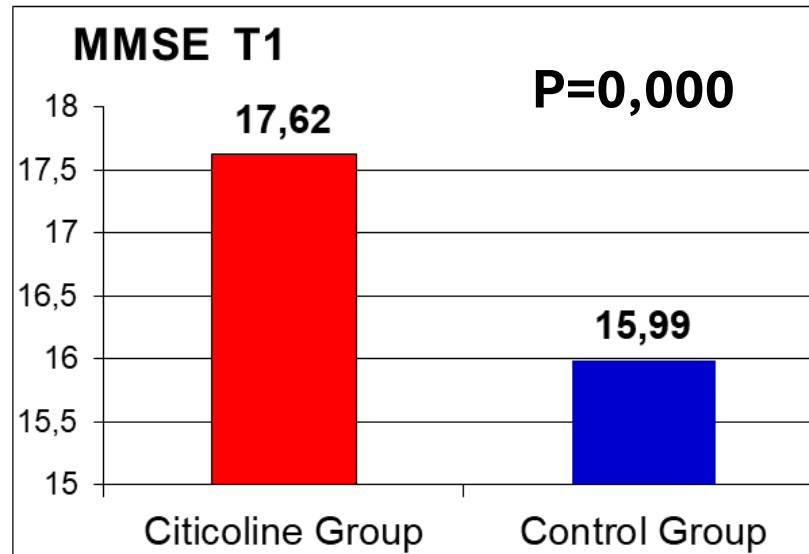
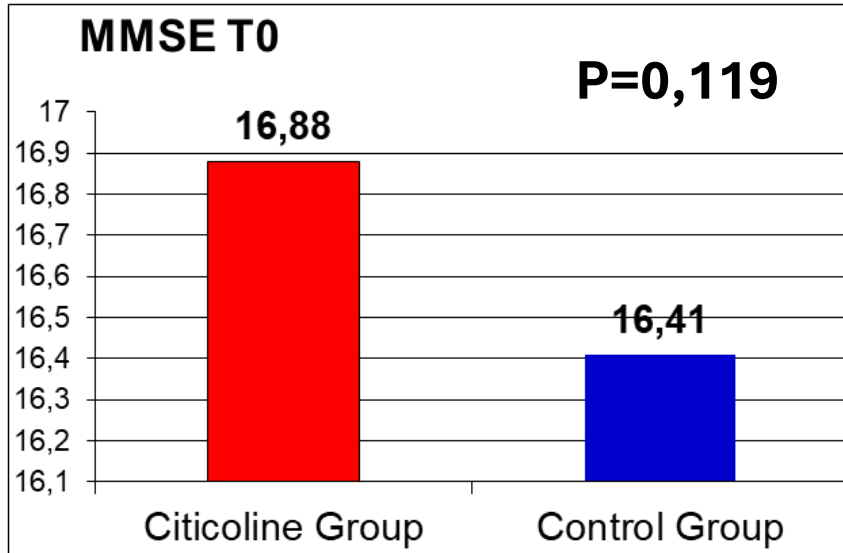
MMSE <sub>c</sub>	Cases (CT), n = 30	Controls (rivastigmine), n = 29	p value
T0	16.04 ± 3.13	14.79 ± 2.75	0.110
T1	16.41 ± 3.26	14.33 ± 2.96	0.014
T2	16.62 ± 3,55	13.20 ± 2.62	0.000

## Conclusions

- The CITIRIVAD Study shows that the association of citicoline to the AChEI rivastigmine may represent an option to prolong or even **potentiate beneficial effects of cholinergic therapies in AD and MD, when concomitant ischemic cerebrovascular injuries are found.**
- The combined treatment rivastigmine + CDPcholine was **advantageous in terms of cognitive performances versus patients treated with rivastigmine only, both in the AD and in the MD groups.** Furthermore, in the AD group the increasing trend in MMSE score appeared to be statistically significant, even if it was similar in MD patients.
- If we think to about the pathogenetic mechanisms causing AD and MD, we could hypothesize that **a more prolonged treatment points out the advantage of combined treatment.**
- The **results are very positive**, even if we need to take into account the poor sample size, and its features of being a retrospective and observational study.
- Future perspectives could be a similar study on a wider number of patients affected with AD or MD treated with other AchEIs (galantamine, donepezil) and the possible differences in response rate among the various AchEIs.

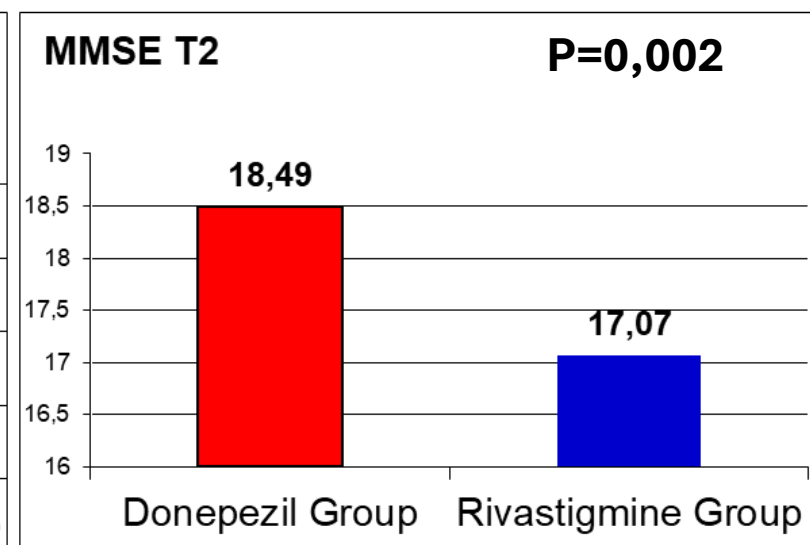
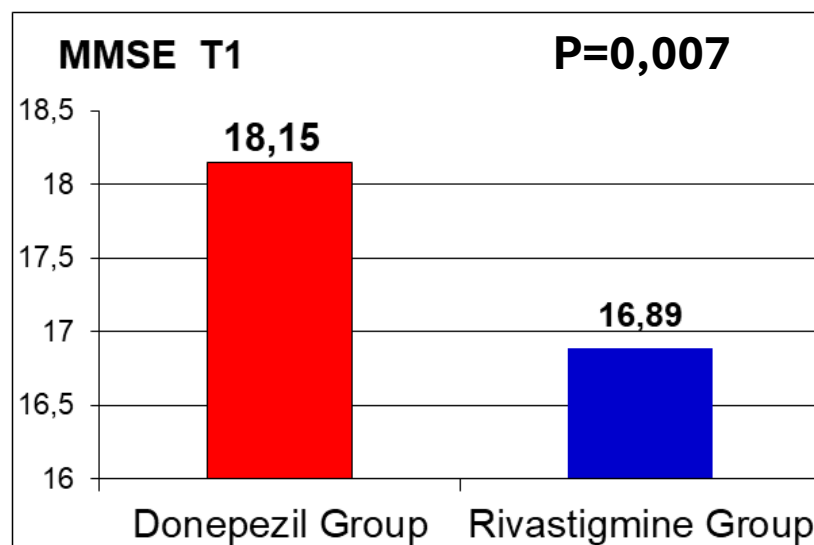
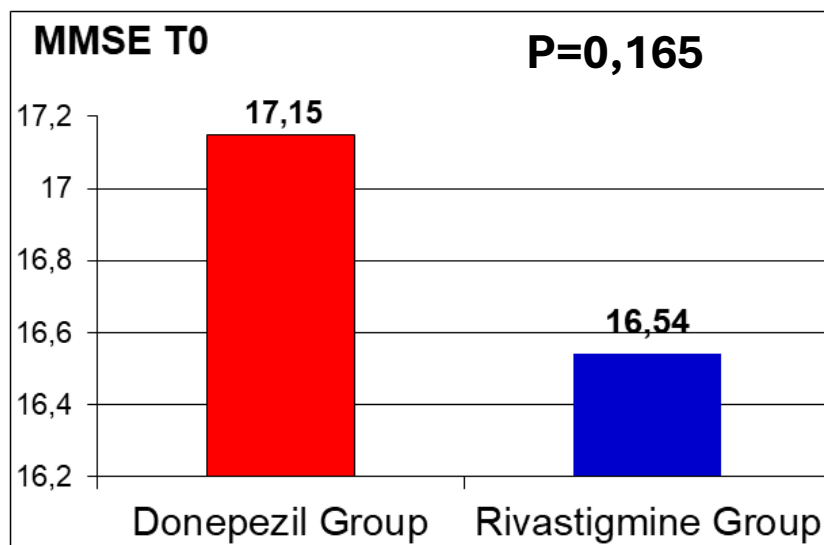
The Citicholinage Study: Citicoline  
Plus Cholinesterase Inhibitors in Aged  
Patients Affected with Alzheimer's  
Disease Study

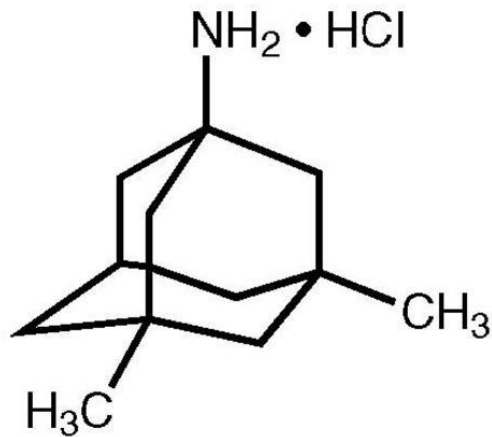
# MMSE at Baseline, T1 and T2



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

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





Memantine hydrochloride

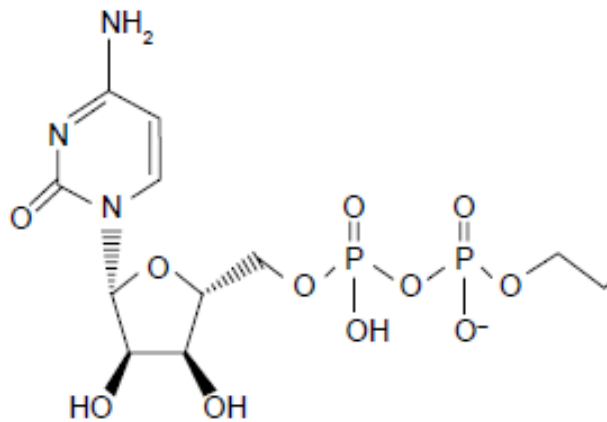


Figure 1 Citicoline's chemical structure.

*Introduction:* Citicoline can have beneficial effects both in degenerative and in vascular cognitive decline; it works through an increase in acetylcholine intrasynaptic levels and promoting phospholipid synthesis, (chiefly phosphatidylcholine), cellular function, and neuronal repair. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist used for the treatment of mild to moderate Alzheimer's disease (AD). When co-administered they could have a synergistic action in patients affected with AD and mixed dementia (MD) too.

*Scope:* The aim of the present study was to show the effectiveness of oral citicoline plus memantine in patients affected with AD and MD.

*Patients and methods:* This was a retrospective study between 2015 and 2017 on 126 patients aged 65 years old or older affected with AD or MD (mean age  $80.7 \pm 5.2$  years old). The study involved four different centers for dementia all over Italy. Diagnosis of AD was made according to clinical symptoms, neuropsychological tests and brain imaging. Diagnosis of MD was made when symptoms typical of AD such as memory loss were associated to symptoms due to cerebrovascular deficits, i.e., impaired judgement, ability to make decisions, plan or organize, and brain imaging. 58 patients were treated with memantine (group A), 68 patients with memantine plus citicoline 1 g/day given orally (group B). In both groups memantine dosage was 10–20 mg/day according to its tolerability. 24 patients of group A and 29 patients of group B were affected with MD. Cognitive functions were assessed by MMSE, daily life functions by ADL and IADL, behavioral symptoms by NPI, comorbidities by CIRS, and mood by GDS-short form. Tests were administered at baseline (T0), after 6 (T1), and 12 months (T2). The primary outcomes were the effects of combined treatment versus memantine alone on cognitive functions assessed by MMSE. The secondary outcomes were the possible side effects or adverse events of combination therapy versus memantine alone, influence on daily life functions and behavioral symptoms.

*Results and conclusions:* Patients treated with citicoline plus memantine showed an increase in MMSE between T0 and T1 ( $16.6 \pm 2.9$  vs  $17.4 \pm 2.7$ ) and between T1 and T2 ( $17.4 \pm 2.7$  vs  $17.7 \pm 2.8$ ).

The difference in MMSE score was significant when comparing the two groups, both at T1 ( $p = 0.003$ ) and T2 ( $p = 0.000$ ).

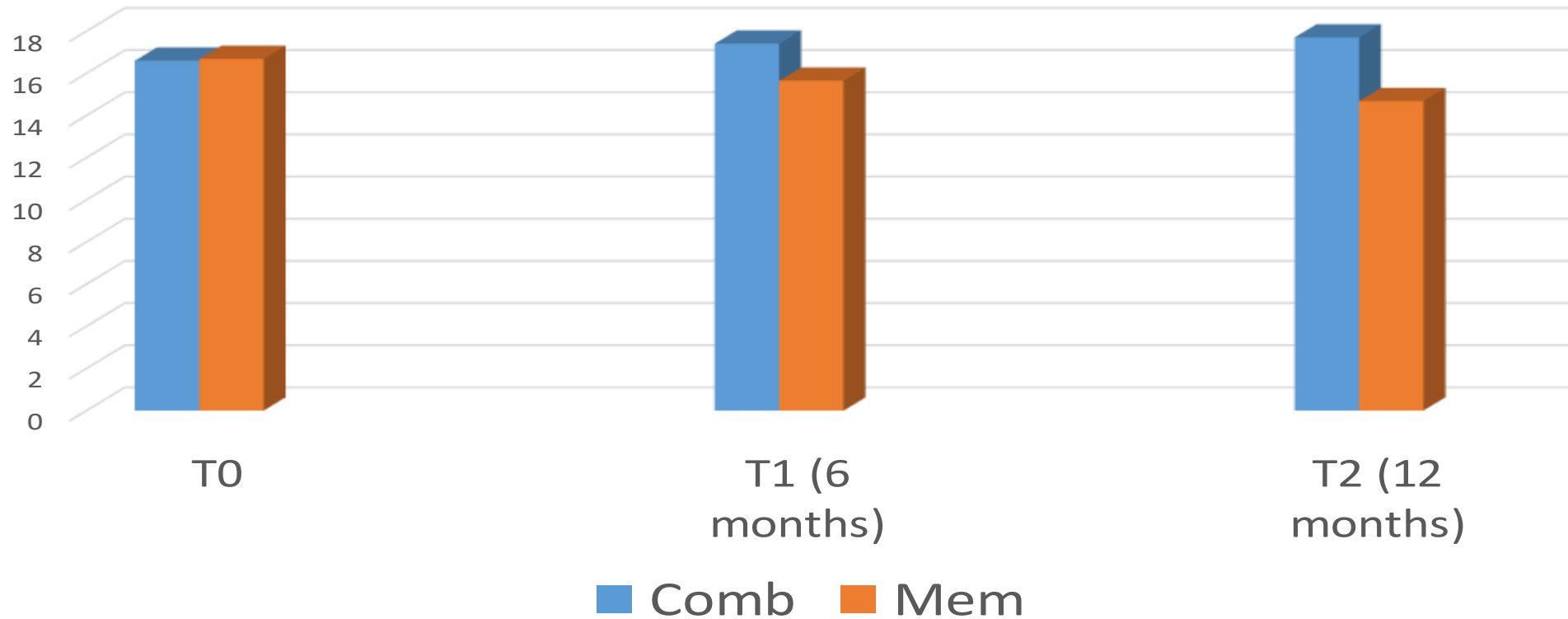
Since it is important to maximize the pharmacological means in AD and MD, the present study encourages the role of combined administration of memantine plus citicoline in disease management and in slowing down the progression of disease.



### The CITIMEM study: A pilot study. Optimizing pharmacological treatment in dementia



Pietro Gareri<sup>a,\*</sup>, Antonino Maria Cotroneo<sup>b</sup>, Giuseppe Orsitto<sup>c</sup>, Salvatore Putignano<sup>d</sup>



**320 patients**

4 CDCD - retrospective study between 2016 and 2018

### Inclusion criteria

- age of 65 years or older;
- people affected with AD;
- people had to be on treatment with Memantine plus an AchEI or Memantine + an AchEI + Citicoline 1g since at least three months, from scheduled start.

### Exclusion criteria

- patients with other neurological disorders, severe psychiatric conditions, other severe comorbidities, or taking medications potentially able to interfere with the results of the study (for example, drugs used for cognitive impairment, i.e. cognitive enhancers, such as choline alfoscerate, choline bitartrate, L-a-glycerophosphorylethanolamine, homotaurine, etc.).

**169 patients**  
mean age  $78.3 \pm 5.68$  years old

### 84 AD pts group A – Combined therapy with citicoline)

39 F – 45 M ( $77.7 \pm 5.47$  years old)  
Memantine 10-20 mg +  
Donepezil 5-10 mg or  
Rivastigmine transdermal patches 4.6-9.5-13.3 mg  
+ Citicoline 1g

### 85 AD pts group B

47 F – 38 M ( $78.8 \pm 5.89$  years old)  
Memantine 10-20 mg +  
Donepezil 5-10 mg or  
Rivastigmine transdermal patches 4.6-9.5-13.3 mg

#### MMSEc

T0 $15.85 \pm 2.86$	baseline
T1 $16.39 \pm 2.93$	6 months
T2 $16.43 \pm 3.08$	12 months

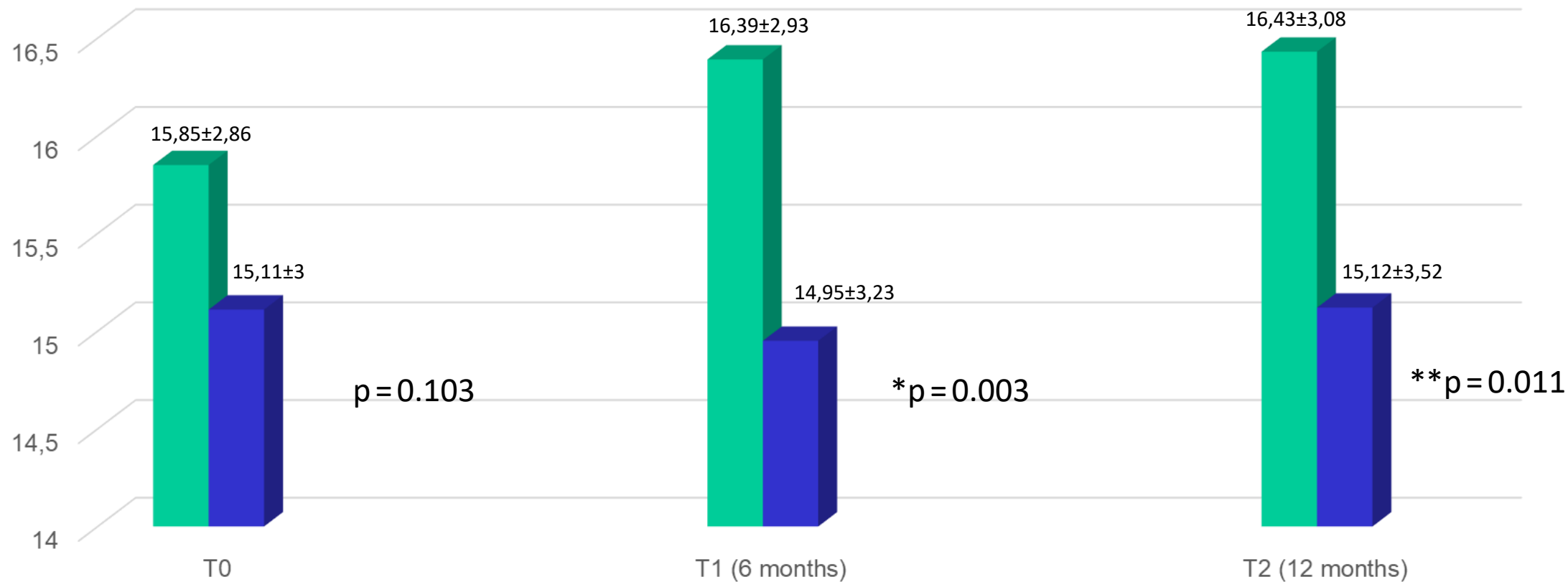
p 0.003  
p 0.011

#### MMSEc

T0 $15.11 \pm 3$	baseline
T1 $14.95 \pm 3.23$	6 months
T2 $15.12 \pm 3.52$	12 months

**GDS score significantly improved in group A after 6 months.**  
**No differences between T1 and T2**

**EuroQoL score significantly improved in group A after 6 and 12 months**



■ Group A ■ Group B

**Gareri et al., Alzheimer's & Dementia, 2020**

Tabella 2. Gli studi sulle terapie di combinazione con citicolina pubblicati ad oggi.

AD = Demenza di Alzheimer; MD = demenza mista; AchEIs = inibitori dell'acetilcolinesterasi

Nome dello studio	Tipo di studio	Pazienti e tipo di demenza (n)	Terapia di combinazione	Baseline (punteggio MMSE) Casi vs controlli	3 mesi (punteggio MMSE) Casi vs controlli	6 mesi (punteggio MMSE) Casi vs controlli	9 mesi (punteggio MMSE) Casi vs controlli	12 mesi (punteggio MMSE) Casi vs controlli
<b>CTIRIVAD</b>	Retrospectivo Multicentrico Caso-controllo	n = 174 AD; MD	Citicolina 1g + rivastigmina	16.04±3.13	<b>16.41±3.26*</b>	//	<b>16.62±3.55*</b>	//
				14.79±2.75	<b>14.33±2.96</b> <b>p=0.001</b>	//	<b>13.2±2.62</b> <b>p=0.000</b>	//
<b>CTICHOLINAGE</b>	Retrospectivo Multicentrico Caso-controllo	n = 448 AD	Citicolina 1g + AchEIs	16.88±3.38	<b>17.62±3.64*</b>	//	<b>17.89±3.54*</b>	//
				16.41±2.97	<b>15.99±3.16</b> <b>p=0.000</b>	//	<b>15.41±3.16</b> <b>p=0.000</b>	//
<b>CTIMEM</b>	Retrospectivo Multicentrico Caso-controllo	n = 126 AD; MD	Citicolina 1g + memantina	16.6 ± 2.9	//	<b>17.4 ± 2.7*</b>	//	<b>17.7 ± 2.8*</b>
				16.6±2.9	//	<b>15.6±2.9</b> <b>p=0.003</b>	//	<b>14.6±3</b> <b>p=0.000</b>
<b>CTIDEMAGE</b>	Retrospectivo Multicentrico Caso-controllo	n = 169 AD	Citicolina 1g + AchEIs + memantina	15.85 ± 2.86	//	<b>16.39 ± 2.93*</b>	//	<b>16.43±3.08*</b>
				15.11 ± 3	//	<b>14.95 ± 3.23</b> <b>p=0.003</b>	//	<b>15.12±3.52</b> <b>p=0.011</b>
<b>CTIMERIVA</b>	Retrospectivo Multicentrico Caso-controllo	n = 104 AD	Citicolina 1g + memantina + rivastigmina	13.63 ± 2.46	//	<b>14.17 ± 2.24*</b>	//	<b>14.32 ± 2.53*</b>
				14.25 ± 2.66	//	<b>14.24 ± 2.88</b> <b>T0vsT1 p=0.008</b>	//	<b>14.00 ± 2.97</b> <b>T0vsT2 p=0.002</b>
<b>CTIMEA</b>	Retrospectivo Multicentrico Caso-controllo	n = 170 AD	Citicolina 1g + memantina + AchEIs	14.88 ± 2.95	//	14.95 ± 2.63	//	<b>15.09 ± 3.00*</b>
				14.37 ± 2.63	//	14.19 ± 2.81	//	<b>14.03 ± 2.92</b> <b>p=0.024</b>

**Background:** Citicoline is a naturally occurring compound with pleiotropic effects on neuronal function and cognitive processes.

**Objective:** Based on previous studies, which shed light on the positive effects of citicoline 1 g when combined with acetylcholinesterase inhibitors (AChEIs) and/or memantine, we further investigated the benefits of citicoline in combination therapy in Alzheimer's disease and mixed dementia.

**Methods:** We integrated the datasets of CITIMEM and CITIDEMAGE, increasing the overall sample size to enhance statistical power. We analyzed data from these two investigator-initiated studies involving 295 patients. The primary outcome was the assessment over time of the effects of combined treatment versus memantine given alone or AChEI plus memantine on cognitive functions assessed by Mini-Mental State Examination (MMSE). The secondary outcomes were the influence of combined treatment on daily life functions, mood, and behavioral symptoms assessed by activities of daily life (ADL) and instrumental ADL, Geriatric Depression Scale, and Neuropsychiatric Inventory Scale. One-hundred-forty-three patients were treated with memantine and/or AChEI (control group), and 152 patients were treated with memantine and/or AChEI plus citicoline 1 g/day orally (Citicoline group).

**Results:** A significant difference in MMSE score was found in the average between the two groups of treatment at 6 and 12 months.

**Conclusions:** This study confirmed the effectiveness of combined citicoline treatment in patients with mixed dementia and Alzheimer's disease, with a significant effect on the increase of MMSE score over time. The treated group also showed a significant reduction in the Geriatric Depression Scale and a significant increase in the instrumental ADL scale.

Table 1  
Summary of baseline characteristics per treatment

	Control ( <i>n</i> = 143)	Citicoline ( <i>n</i> = 152)	Total ( <i>n</i> = 295)
Age (y), mean (SD)	79.98 (6.01)	79.38 (5.26)	79.67 (5.64)
Sex, <i>n</i> (%)			
Female	83 (58)	85 (56)	168 (57)
Male	60 (42)	67 (44)	127 (43)
Years of education in classes, <i>n</i> (%)			
1–5	31 (22)	32 (21)	63 (21)
5–7	52 (36)	58 (38)	110 (37)
7–8	3 (2)	4 (3)	7 (2)
≥8	57 (40)	58 (38)	115 (39)
MMSE T0, mean (SD)	15.58 (2.95)	16.28 (2.89)	15.94 (2.93)
CIRS T0, mean (SD)	3.09 (1.06)	3.6 (1.04)	3.35 (1.08)
ADL T0, mean (SD)	3.24 (1.03)	3.34 (1.08)	3.29 (1.06)
IADL T0, mean (SD)	2.13 (1.12)	2.21 (1.25)	2.17 (1.19)
NPI T0, mean (SD)	11.56 (7.51)	13.03 (8.76)	12.32 (8.2)
GDS T0, mean (SD)	2.76 (1.34)	2.55 (1.33)	2.65 (1.34)

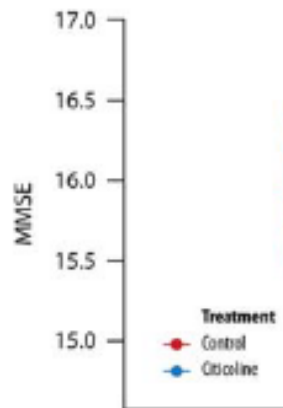


Fig. 1. The mean difference in the average MMSE score between the two groups of treatment at each time point (T1, 6 months and T2, 12 months) (t-test with a 5% significance level). Rank Sum Tests with Bonferroni's correction were used to compare the two groups of treatment at baseline (T0).

**Supplementary Figure 1. Two-way ANOVA with repeated measures over time (MMSE versus time and treatment).** At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), we found a significant difference in the average between the two groups of treatment (t-test with a 5% significance level).

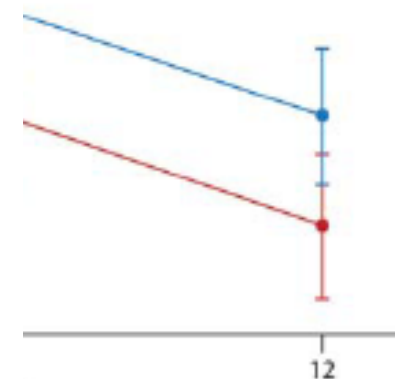
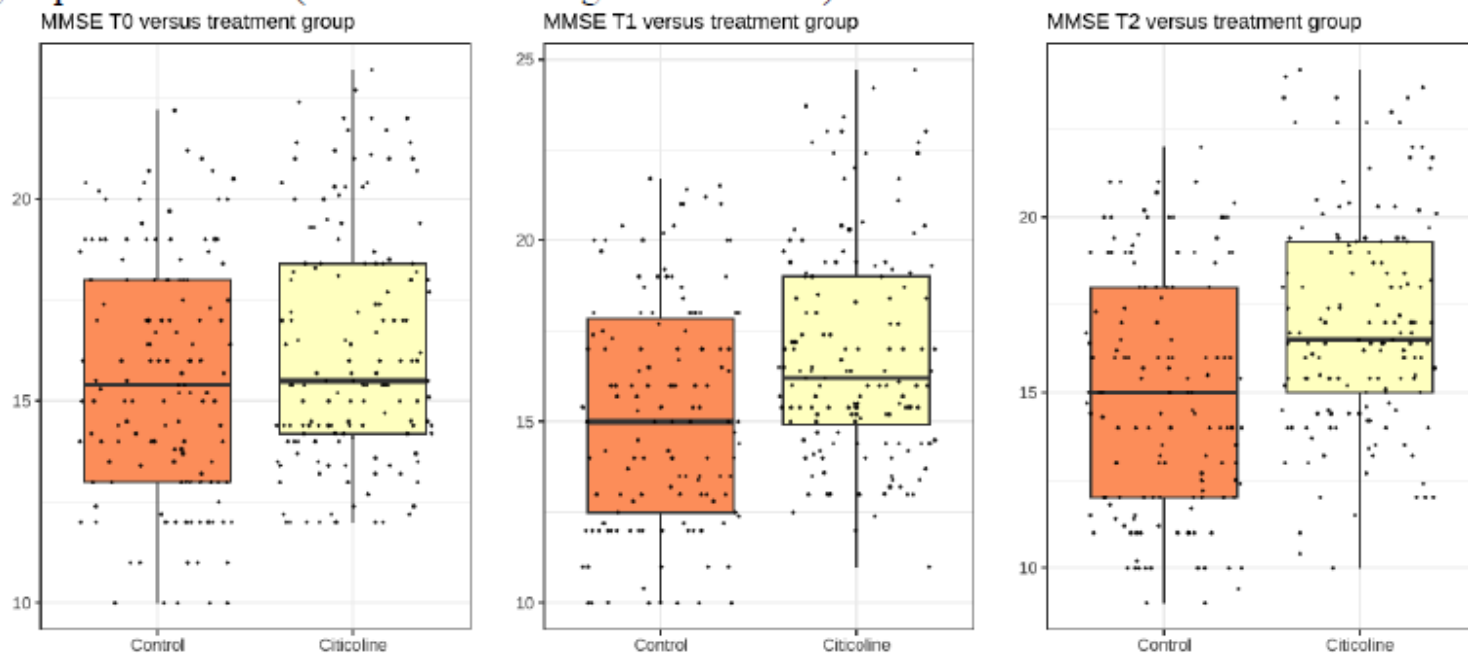


Fig. 2. The mean difference in the average MMSE score between the two groups of treatment at each time point (T1, 6 months and T2, 12 months) (t-test with a 5% significance level). Rank Sum Tests with Bonferroni's correction were used to compare the two groups of treatment at baseline (T0). No significant difference was found between the two groups of treatment at 12 months (t-test with a 5% significance level;  $p = 0.277$ ).

- Citicolina nei disturbi comportamentali?

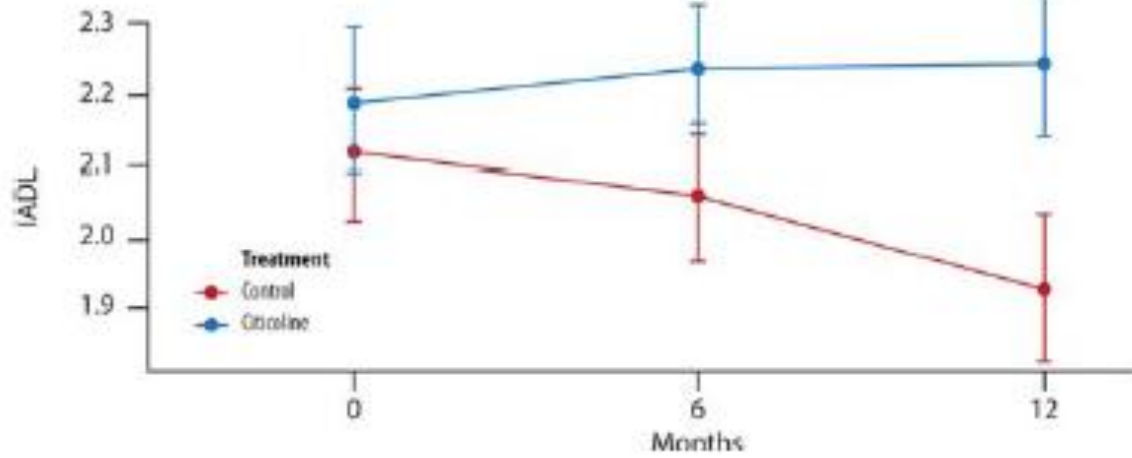


Fig. 3. **The mean change in IADL score over time.** Difference in the average between the two groups of treatment at (T1, 6 months and T2, 12 months) (*t*-test with a 5% significance level).  $p = 0.189$  T1 versus treatment group;  $*p = 0.032$  T2 versus treatment group.

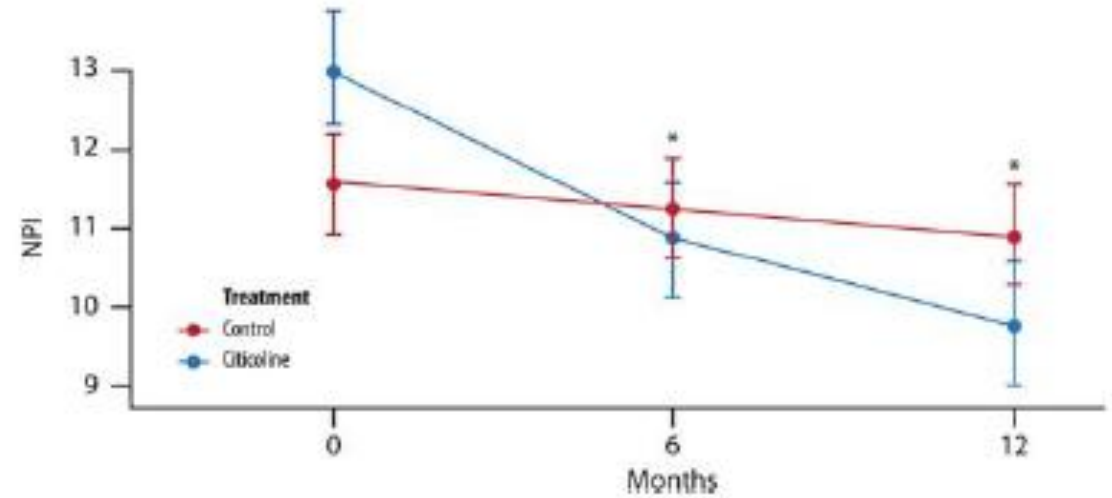
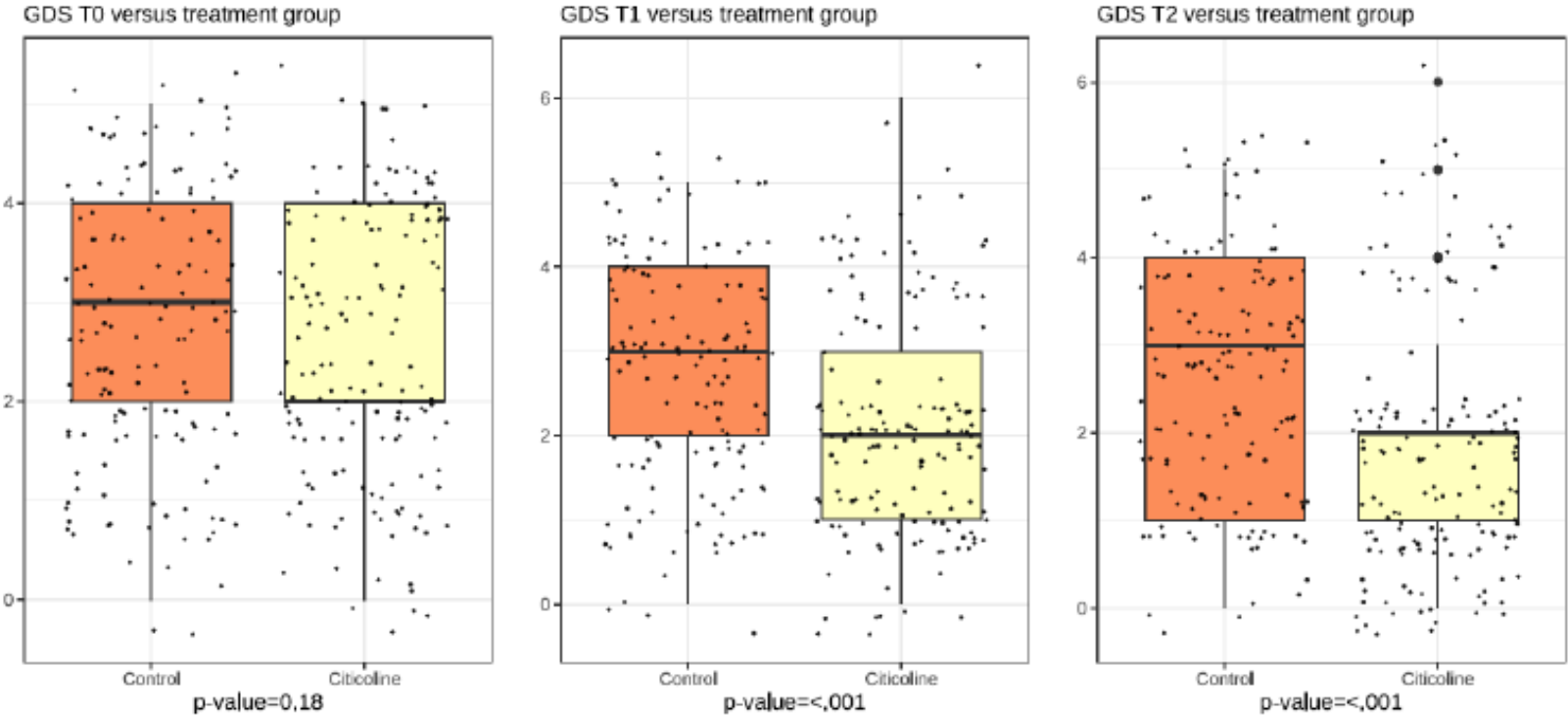


Fig. 4. **The mean change in NPI score over time.** Difference in the average between the two groups of treatment at each time point (T1, 6 months and T2, 12 months) (*t*-test with a 5% significance level).  $p = 0.688$  T1 versus treatment group;  $p = 0.275$  T2 versus treatment group.

**Figure 5. Two-way ANOVA with repeated measures over time (GDS versus time and treatment).** At each time point (indicated in the plot with T0, baseline, T1, 6 months and T2, 12 months), we found a significant difference in mean between the two groups of treatment (t-test with a 5% significance level).



<b>Introducción</b>	S1	<b>Farmacocinética</b>	S26
<hr/>		Curvas de niveles plasmáticos. Biodisponibilidad	S26
<b>Acciones farmacológicas</b>	S2	Difusión tisular y distribución. Transporte y metabolismo	S27
Lesiones traumáticas y edema cerebral experimental	S2	Vía y cinética de eliminación	S28
Hipoxia e isquemia cerebral	S7	<hr/>	
Transmisión sináptica, sistemas de señalización intracelular y niveles de neurotransmisores	S13	<b>Experiencia clínica</b>	S29
Rendimientos de aprendizaje, memoria y envejecimiento cerebral	S21	Traumatismos craneoencefálicos y secuelas	S29
Síndrome de abstinencia experimental e intoxicaciones	S24	Patología vascular cerebral aguda y secuelas	S38
<hr/>		Trastornos cognitivos	S49
<b>Toxicidad</b>	S25	Otras experiencias clínicas	S58
Toxicidad aguda	S25	Seguridad	S62
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Toxicidad crónica	S26	<b>Conclusiones</b>	S63
Teratogenicidad	S26	<hr/>	
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## **Il presente**



- **Ottimizzare le terapie che possano in qualche modo rallentare la progressione della malattia**
- **Approccio colinergico associando un precursore colinergico come citicolina può attualmente essere una valida alternativa per cercare di ritardare la progressione del declino cognitivo nell'AD e nella MD**

## **Il futuro....**

- **Ricerca molecole con evidenza di efficacia e tollerabilità....**
- **Lecanemab? Donanemab?**
- **Altro?**

## RESEARCH ARTICLE

STING deletion protects against amyloid  $\beta$ -induced  
Alzheimer's disease pathogenesis

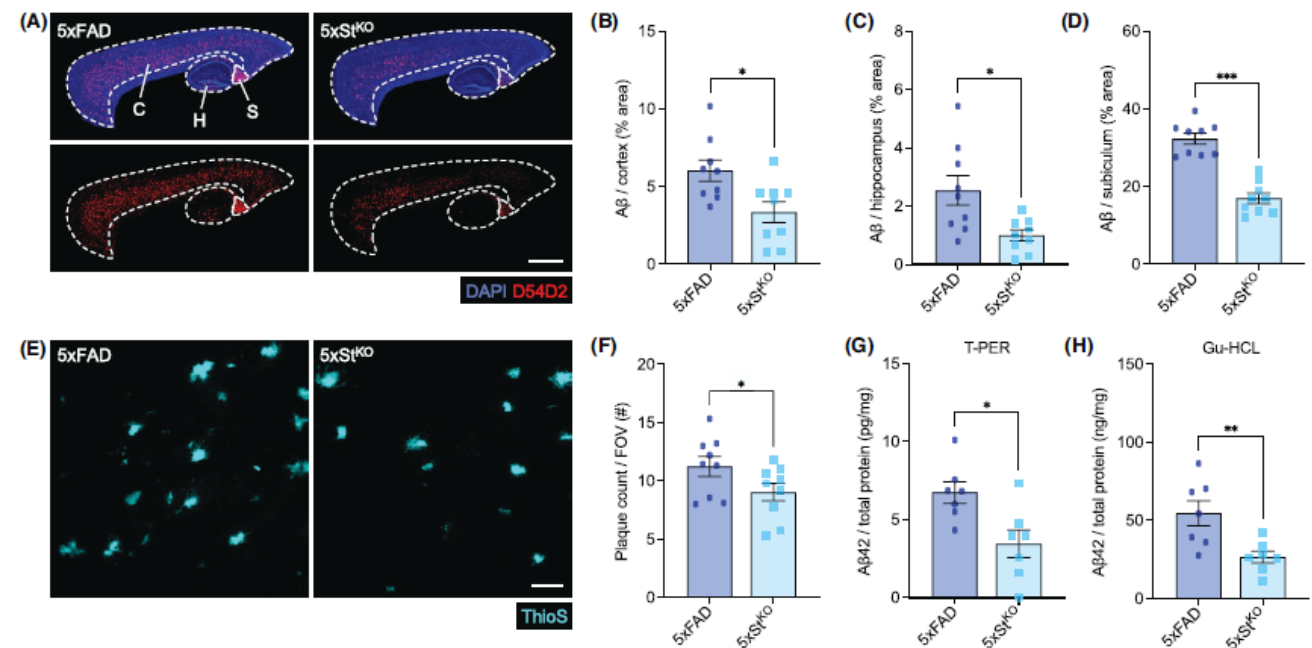
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## Highlights

- Stimulator of interferon genes (STING) deficiency in the 5xFAD mouse model of Alzheimer's disease-related amyloidosis results in decreased amyloid beta ( $A\beta$ ) deposition and altered microglial activation status.
- Protection against amyloidosis in STING-deficient 5xFAD mice is associated with decreased expression of genes involved in type I IFN signaling, improved neuronal health, and reduced levels of oxidative stress.
- Loss of STING in 5xFAD mice leads to improved spatial learning and memory.





**A DOCTOR= working with your own  
EMOTIONS, cultivating your PASSION and the  
SCIENCE of the profession, knowing that you  
do NOT know**

**GRAZIE PER L' ATTENZIONE**