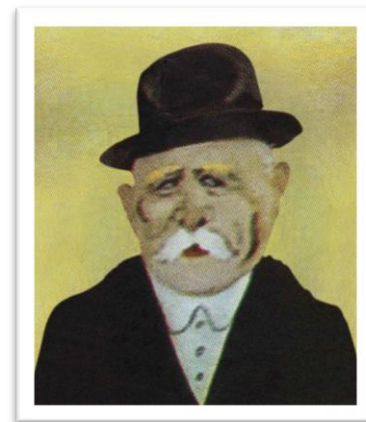


SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA  
Azienda Unità Sanitaria Locale della Romagna

U.O. Anziani e Disabili fisici e sensoriali – Rimini



Ferrara, 24 ottobre 2014

## LA “TERAPIA MULTIFATTORIALE” NEL DETERIORAMENTO COGNITIVO DELL’ANZIANO: QUALI EVIDENZE ?

Stefano De Carolis

Responsabile Aziendale del Progetto Demenze per il territorio della Provincia di Rimini

► **L-acetilcarnitina  
e trattamento della  
demenza senile**

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Congresso nazionale di



UNIVERSITÀ  
DEGLI STUDI  
DI FERRARA  
EX LABORE FRUCTUS

# Storia della Farmacia

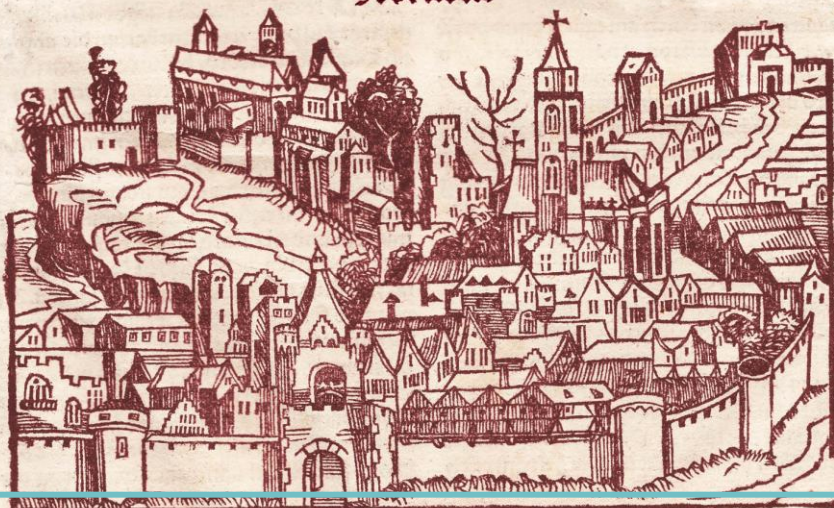


## Musei farmaceutici e di arte sanitaria:

la storia sussurrata dai "testimoni" del tempo

20-21 Settembre 2014

Ferrara



Chiostro di Santa Maria delle Grazie - via Fossato di Mortara 17/19

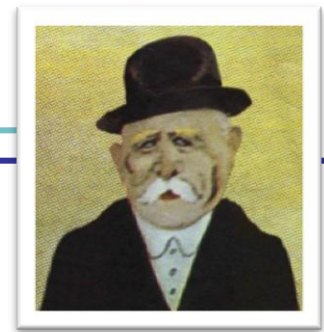
Ferrara, Hartmann Schedel, Schedelsche Weltchronik, 1497. Cortesia A.C. Veronese



Ferrara, 21 settembre 2014



# Farmacodinamica e farmacocinetica

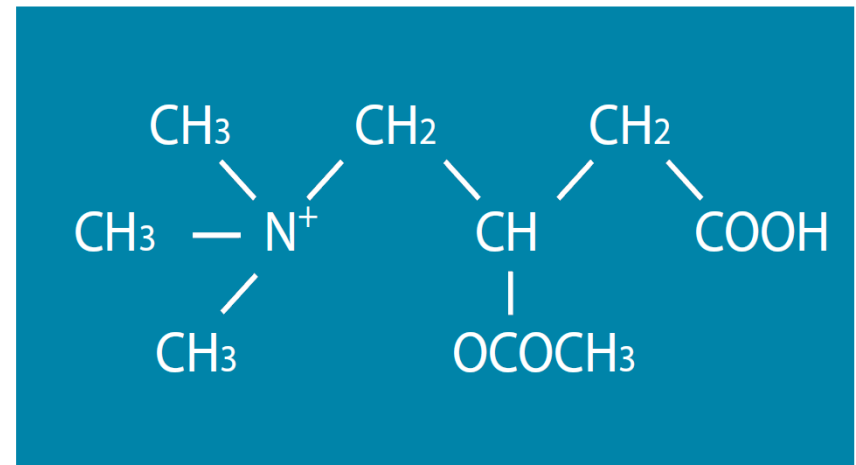


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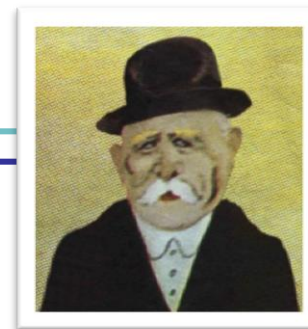
▶ Acetyl-L-carnitine (ALC, ALCAR, LAC) is an ester of the trimethylated amino acid, L-carnitine (LC), and is **synthesized** in the human brain, liver, and kidney by the enzyme ALC-transferase.

▶ ALC facilitates the uptake of acetyl CoA into the **mitochondria** during fatty acid oxidation, enhances **acetylcholine** production, and stimulates protein and membrane phospholipid **synthesis**. ALC, similar in structure to acetylcholine, also exerts a **cholinomimetic** effect.

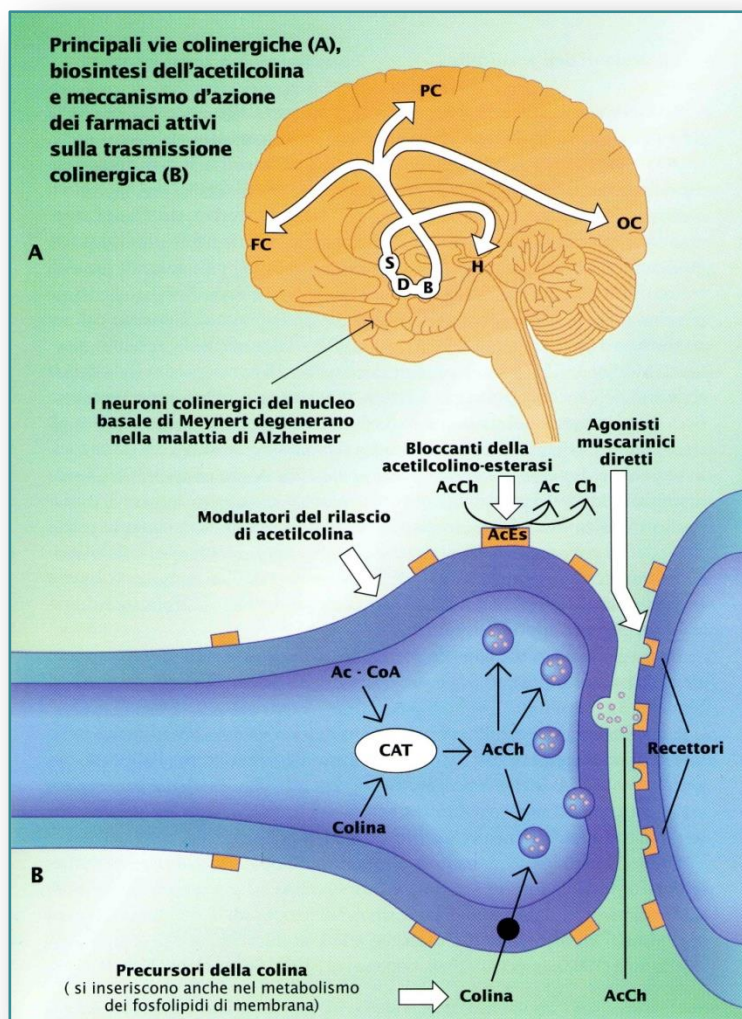
▶ ALC and LC are **adsorbed** in the jejunum by simple diffusion. ALC readily crosses the **blood-brain barrier**. LC and its esters undergo minimal metabolism and are subsequently **excreted** in the urine via renal tubular reabsorption. The rate of clearance increase with the plasma concentration of these substances.



# L'approccio colino-mimetico



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FC = corteccia frontale  
PC = corteccia parietale  
OC = corteccia occipitale  
H = ippocampo

S = nucleo settale  
D = nucleo della banda diagonale del Broca  
B = nucleo basale di Meynert

AcCh = acetilcolina  
CAT = colina-acetiltransferasi  
Ac-CoA = acetil coenzima A  
AcEs = acetilcolinesterasi

# L'approccio colino-mimetico

## Strategie di intervento farmacologico sul sistema colinergico nella malattia di Alzheimer

### ► STIMOLANTI DELLA FUNZIONE COLINERGICA:

#### 1) Precursori dell'acetilcolina

- a) colina, lecitina
- b) L-acetilcarnitina
- c) L- $\alpha$ -gliceril-fosforilcolina ( $\alpha$ -GFC)
- d) fosfatidilcolina
- e) citidina-5'-difosfocolina (CDP-colina)

#### 2) Modulatore della secrezione e dell'immagazzinamento dell'acetilcolina

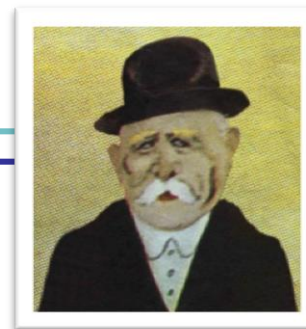
- a) aminopiridine
- b) fosfatidilserina
- c) piracetam

### ► AGENTI COLINERGICI DIRETTI:

#### 1) Inibitori delle colinesterasi (I e II generazione)

#### 2) Agonisti colinergici

- a) muscarinici
- b) nicotinici (inclusa la nicotina)



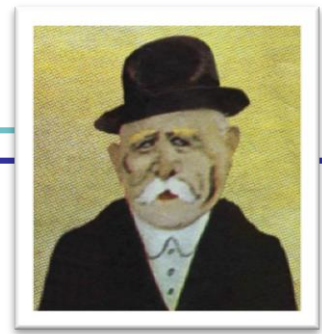
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# L'approccio colino-mimetico



Farmaco	Ditta	Indicazioni	Posologia
BRANIGEN	<i>Segix</i>	Neuropatia diabetica, lesioni meccaniche e infiammatorie tronculari e radicolari del nervo periferico, sindromi involutive primarie o secondarie a vasculopatie cerebrali	0,5-1,5 g al giorno in 2-3 somministrazioni
CEREDOR	<i>Irbi</i>	Coadiuvante nelle sindromi involutive primarie o secondarie a vasculopatie cerebrali	0,5-1,5 g al giorno in 2-3 somministrazioni
NICETILE	<i>Sigma-Tau</i>	Neuropatia diabetica, lesioni meccaniche e infiammatorie tronculari e radicolari del nervo periferico, sindromi involutive primarie o secondarie a vasculopatie cerebrali	0,5-1,5 g al dì in 2-3 somministrazioni
NORMOBREN	<i>Medosan</i>	Sindromi involutive cerebrali su base degenerativa o vascolare	0,5-1,5 g al giorno in 2-3 somministrazioni
ZIBREN	<i>Puropharma</i>	Neuropatia diabetica, lesioni meccaniche e infiammatorie tronculari e radicolari del nervo periferico, sindromi involutive primarie o secondarie a vasculopatie cerebrali	0,5-1,5 g al dì in 2-3 somministrazioni

# Studi piccoli e (in)controllati...



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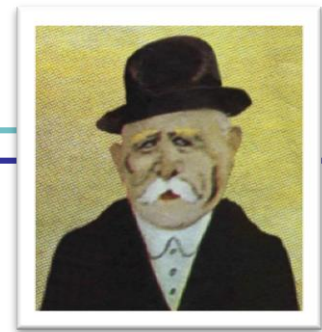
To establish whether acetyl-L-carnitine is clinically effective in the treatment of people with dementia

- ▶ Although currently it is **not in routine clinical use**, ALC has been found to be safe in dementia patients with few reported adverse effects.
- ▶ Clinical studies have been performed in association with the Italian pharmaceutical company producing ALC (Sigma-Tau) **since the 1980s**. These studies were on the cognitive and behavioural effects of ALC in ageing subjects. Encouraging findings in these **small, uncontrolled and often unpublished studies** led to a series of **small controlled studies**, which suggested a possible beneficial role for ALC in slowing down cognitive decline in subjects with cognitive impairment.

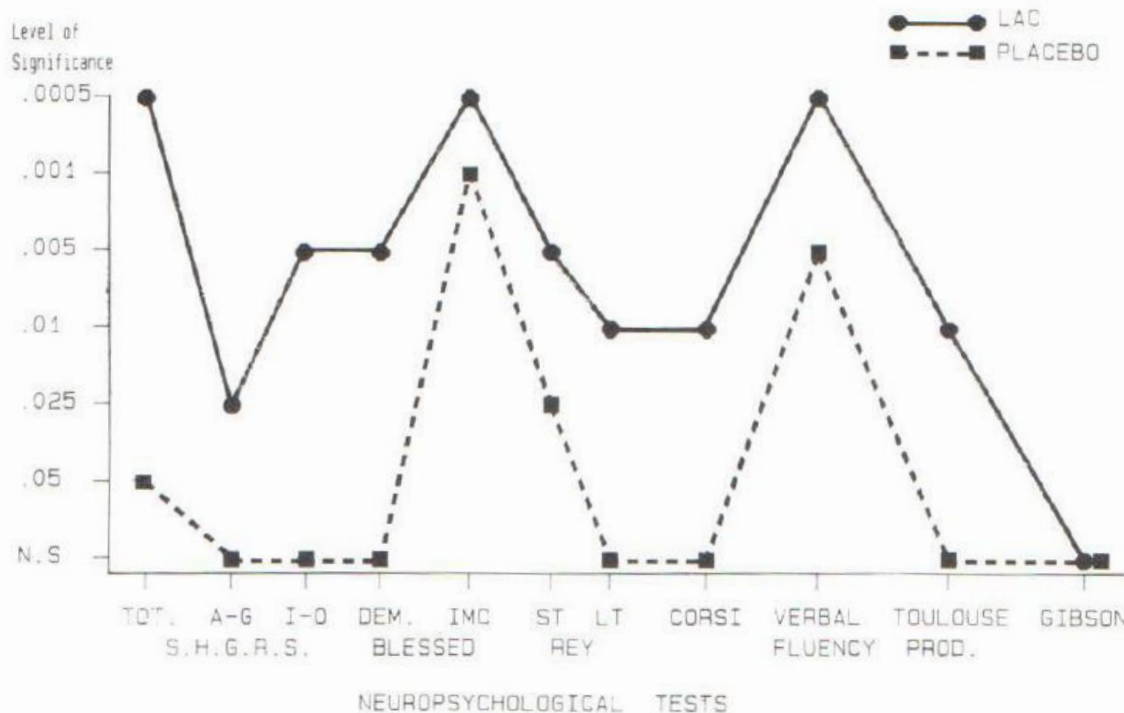




# Studi piccoli e (in)controllati...



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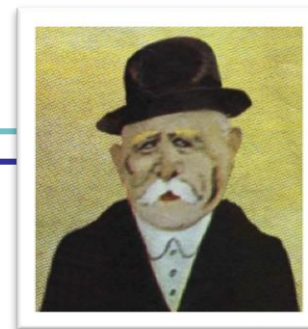
20 males, 38 females  
– LAC 2 g/day for 90 days  
– Placebo for 90 days  
Randomization method  
not described

► LAC-treated patients show a significant statistical improvement in the **behavioral performances** and in **some memory tests**. An evaluation of the results show that ten test were improved in the LAC-treated patients, whereas only four tests were improved in the placebo group.

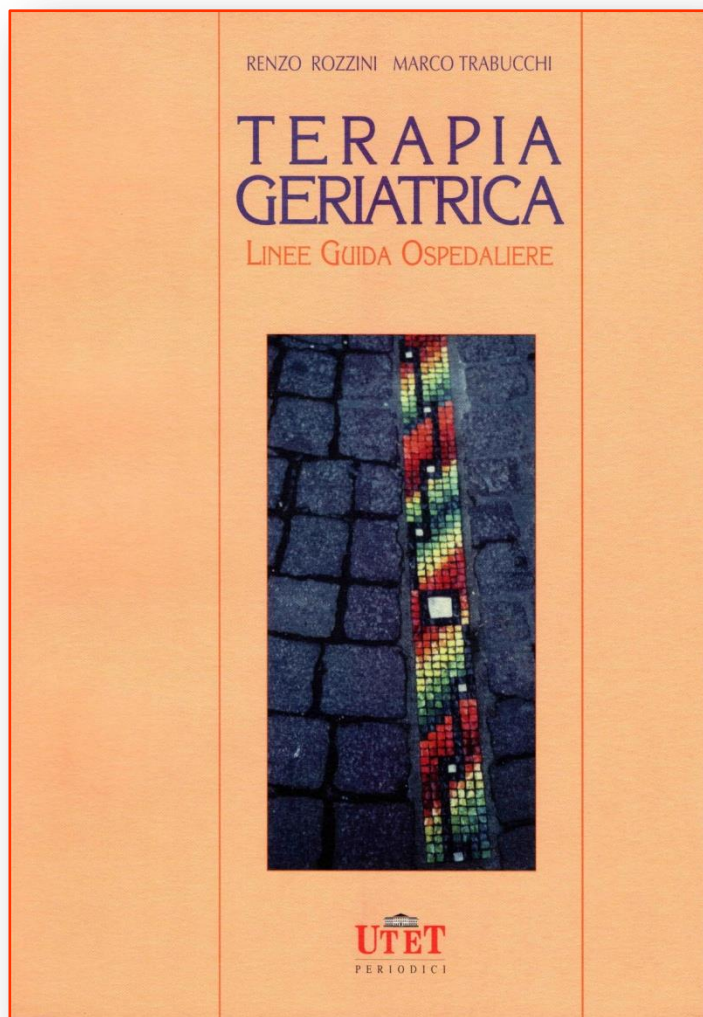
Cucinotta D, Passeri M, Ventura S et al. Multicenter clinical placebo-controlled study with acetyl-L-carnitine (LAC) in the treatment of mildly demented elderly patients. Drug Dev Res 1988; 14 (3-4): 213-216



# Le prime linee guida



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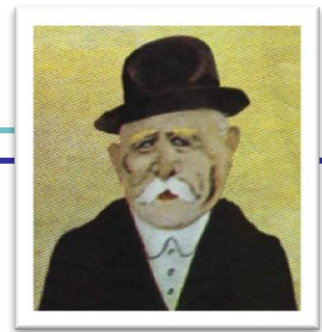
► Altre sostanze sperimentali nell'AD, quali la nimodipina, l'hydergina, l'**l-acetilcarnitina**, sebbene abbiano portato a risultati in parte positivi, non hanno ottenuto l'impatto clinico degli inibitori dell'AChe e vanno perciò considerati **di seconda scelta**, eventualmente utilizzabili in soggetti nei quali gli inibitori dell'AChe sono controindicati o non tollerati.

# La revisione della CUF

31-5-2000

Supplemento ordinario alla GAZZETTA UFFICIALE

Serie generale - n. 125



**CEDEM**

**Centro della Memoria**

## DECRETO 27 gennaio 2000

Programma di revisione per il biennio 2000-2001 di medicinali registrati da più di 10 anni ai sensi all'art. 4 della legge 14 ottobre 1999, n. 362.

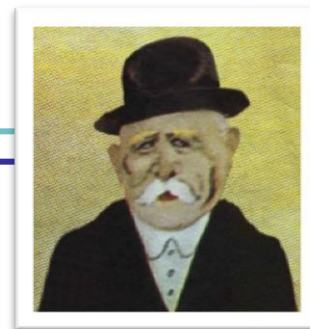
- ▶ L'**invecchiamento** è processo caratteristico degli organismi viventi e di moltissimi non viventi; così un principio attivo, o una specialità farmaceutica sono, nel corso degli anni, resi **vetusti** per nuove conquiste della biomedicina, ridondanza della formula, superamento di efficacia o inappropriata delle indicazioni.
- ▶ Inoltre, anche l'accettazione di principi attivi e specialità da parte delle Autorità sanitarie risale spesso ad epoche in cui i sistemi di valutazione si basavano frequentemente più su **test preclinici, in vitro o in vivo**, e su modelli di valutazione clinica ormai superati e impossibili da collegare ai **principi della medicina basata sull'evidenza** per la individuazione di efficacia clinica in indicazioni terapeutiche ben precise.

# La revisione della CUF

31-5-2000

Supplemento ordinario alla GAZZETTA UFFICIALE

Serie generale - n. 125



**CEDEM**

**Centro della Memoria**

## DECRETO 27 gennaio 2000

Programma di revisione per il biennio 2000-2001 di medicinali registrati da più di 10 anni ai sensi all'art. 4 della legge 14 ottobre 1999, n. 362.

► In base al comma 8 del succitato dispositivo legislativo, la CUF ha “rimodulato” il programma di revisione sistematica in corso, relativo ai farmaci inclusi nelle cosiddette 14 categorie di **farmaci di dubbia efficacia**.

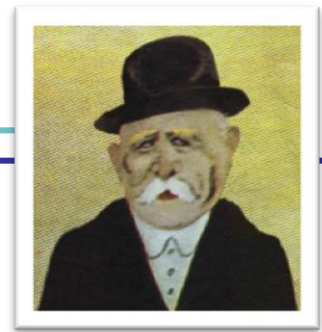
### 1 – Coadiuvanti cerebrovascolari e neurotrofici

► Data la rilevanza delle **indicazioni cliniche vantate**, è necessaria una revisione del profilo di efficacia di tutti i farmaci di questa categoria.

### N06BX Altri psicostimolanti e nootropi

A = Specialità medicinali per le quali si richiede una **verifica** della adeguatezza complessiva dei **dati di efficacia** alla luce delle conoscenze oggi disponibili.

# Descrizione degli studi



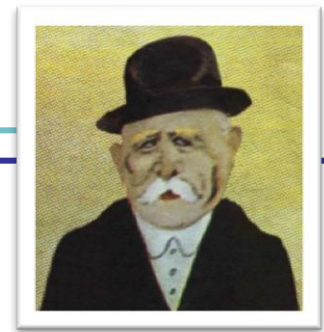
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To establish whether acetyl-L-carnitine is clinically effective in the treatment of people with dementia

- ▶ Sixteen studies fulfilled the inclusion criteria, of which fifteen provided sufficient data to be included in the meta-analysis.
- ▶ ALC appeared to have no common or serious adverse side effects in most studies and a dose titration period was not required. Most studies used a dose of 2 g (range 1 to 3 g).
- ▶ Trial size ranged from 30 to 431 subjects (average 115). The most common duration of treatment was 6 months (range 3 months to 1 year).
- ▶ Most trials recruited subjects aged over 60 years, except Spagnoli 1991 (over 40), Thal 1996 (over 50) and Bellagamba 1991 (over 55). Thal 2000 specifically looked at an early onset group (45 to 65 years).







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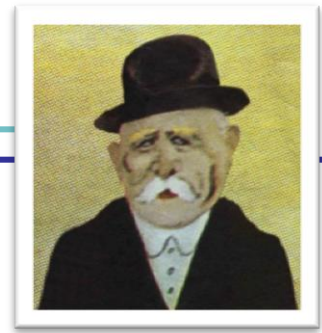
## Clinical diagnosis of Alzheimer's disease:

**Report of the NINCDS-ADRDA Work Group\* under the  
auspices of Department of Health and Human Services  
Task Force on Alzheimer's Disease**

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD;  
Donald Price, MD; and Emanuel M. Stadlan, MD

► In **more recent studies** a diagnosis of dementia was made using accepted criteria such as DSM-IV or NINCDS-ADRDA (McKhann 1984). However for **older studies** DSM / NINCDS-ADRDA criteria were not in common use. In order to ensure all relevant studies were included, criteria that seemed likely to include subjects with dementia were accepted. Most trials included subjects with probable dementia or mild to moderate cognitive decline. Although this review was intended to assess ALC treatment in **all dementia patients**, all studies concentrated on **Alzheimer's dementia** and attempted to exclude other diagnoses.

# Effetti dei trattamenti



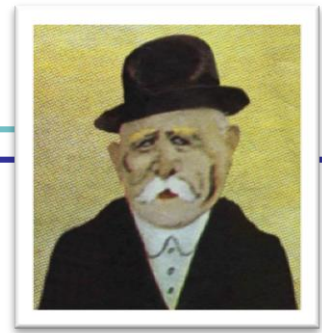
**CEDEM**  
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To establish whether acetyl-L-carnitine is clinically effective in the treatment of people with dementia

- ▶ When considering **clinical global impression (CGI-I)** as a dichotomous variable (numbers improved versus numbers unchanged or worse) there were statistically significant treatment effects in favour of ALC at **12 and 24 weeks** but not at 52 weeks.
- ▶ There was also a statistically significant treatment effect on **MMSE** at **24 weeks** ( $P = 0.02$ ), but not at 12 ( $P = 0.85$ ) or 52 weeks ( $P = 0.14$ ). There is no evidence for an effect on cognition from the meta-analysis of results using **other standardised cognitive scales**.
- ▶ There was no evidence of benefit of ALC in the areas of **severity of dementia, functional ability** or **Clinical Global Impression** as a continuous measure.



# Effetti dei trattamenti



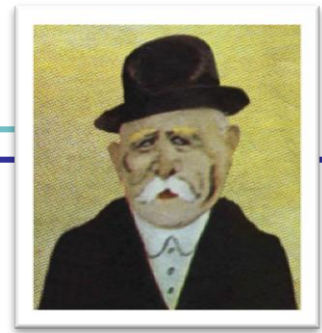
**CEDEM**  
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To establish whether acetyl-L-carnitine is clinically effective in the treatment of people with dementia

- ▶ Drop-outs from trials before completion were also analysed where they were reported. Total **drop-outs for any reason** were not significantly different between the groups. **Drop-outs due to adverse events** did not differ significantly between groups at 12 and 52 weeks.
- ▶ ALC appeared to have no common or serious adverse effects in most studies. The most common adverse effects that may have been related to treatment were **gastrointestinal** e.g. diarrhoea, nausea and vomiting. There were **no statistically significant** treatment effects for numbers of adverse events due to agitation, nausea, aggression, confusion, abdominal discomfort, total adverse events, nor for the numbers of deaths.



# Discussione e conclusioni



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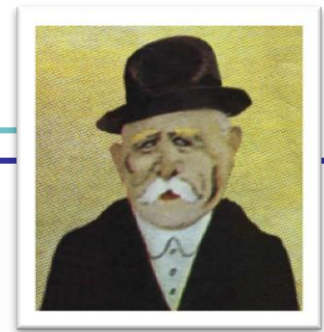
To establish whether acetyl-L-carnitine is clinically effective in the treatment of people with dementia

- ▶ Studies were of different  **durations**, used different  **doses** of ALC, slightly different  **age** groups, different  **criteria for inclusion** and differing  **assessment tools**. This heterogeneity should make one cautious in interpreting the results.
- ▶ Given the large number of comparisons made, the statistically significant results may be  **due to chance**.
- ▶ However, the evidence so far available does not suggest that ALC is likely to prove an important therapeutic agent for the treatment of people with  **dementia**.
- ▶ The evidence of benefit of ALC for people with  **Alzheimer's disease** does not justify recommending its routine clinical use.

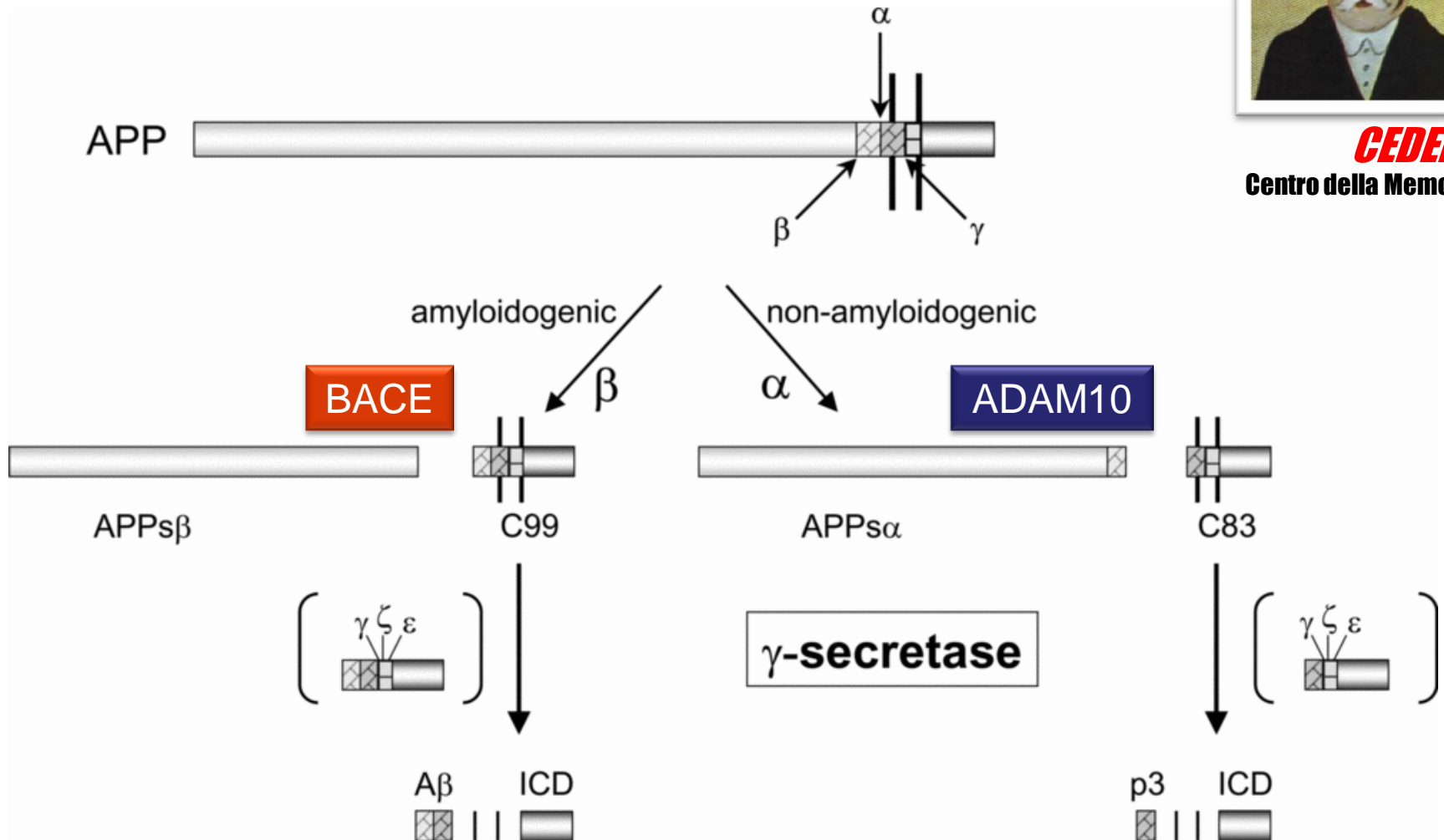




# Metabolismo della APP



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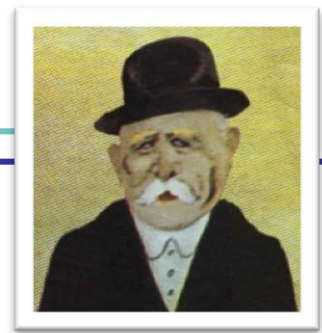
# ALC: effetti antiamiloide



Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: [www.elsevier.com/locate/ejphar](http://www.elsevier.com/locate/ejphar)



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## Behavioural Pharmacology

### Modulatory effect of acetyl-L-carnitine on amyloid precursor protein metabolism in hippocampal neurons

Roberta Epis <sup>a,1</sup>, Elena Marcello <sup>a,1</sup>, Fabrizio Gardoni <sup>a</sup>, Annalisa Longhi <sup>a</sup>, Menotti Calvani <sup>b</sup>, Maurizio Iannuccelli <sup>b</sup>, Flaminio Cattabeni <sup>a</sup>, Pier L. Canonico <sup>c</sup>, Monica Di Luca <sup>a,\*</sup>

<sup>a</sup> Department of Pharmacological Sciences and Center of Excellence on Neurodegenerative Diseases, University of Milan, Milan, Italy

<sup>b</sup> Scientific Department, Sigma Tau I.F.R. S.p.A., via Pontina km 30.400, 00040 Pomezia, Rome, Italy

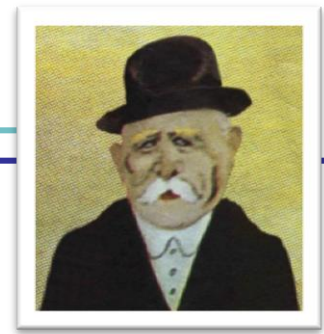
<sup>c</sup> DiSCAFF&DFB Center, Università del Piemonte Orientale, Novara, Italy

- ▶ We found that ALC treatment stimulates  **$\alpha$ -secretase activity** and physiological APP metabolism. In particular, ALC favors the delivery of **ADAM10** (a disintegrin and metalloproteinase 10, the most accredited candidate for  $\alpha$ -secretase) to the post-synaptic compartment, and consequently positively modulates its enzymatic activity towards APP.
- ▶ ALC can **directly influence** the primary event in Alzheimer's disease pathogenesis, i.e. the **Amyloid  $\beta$  cascade**, promoting  $\alpha$ -secretase activity and directly affecting the release of the non amyloidogenic metabolite.

Epis R, Marcello E, Gardoni F, et al. Modulatory effect of acetyl-L-carnitine on amyloid precursor protein metabolism in hippocampal neurons. Eur J Pharmacol 2008; 597 (1-3): 51-56

# ALC: antiossidante mitocondriale

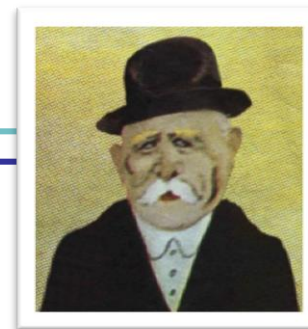
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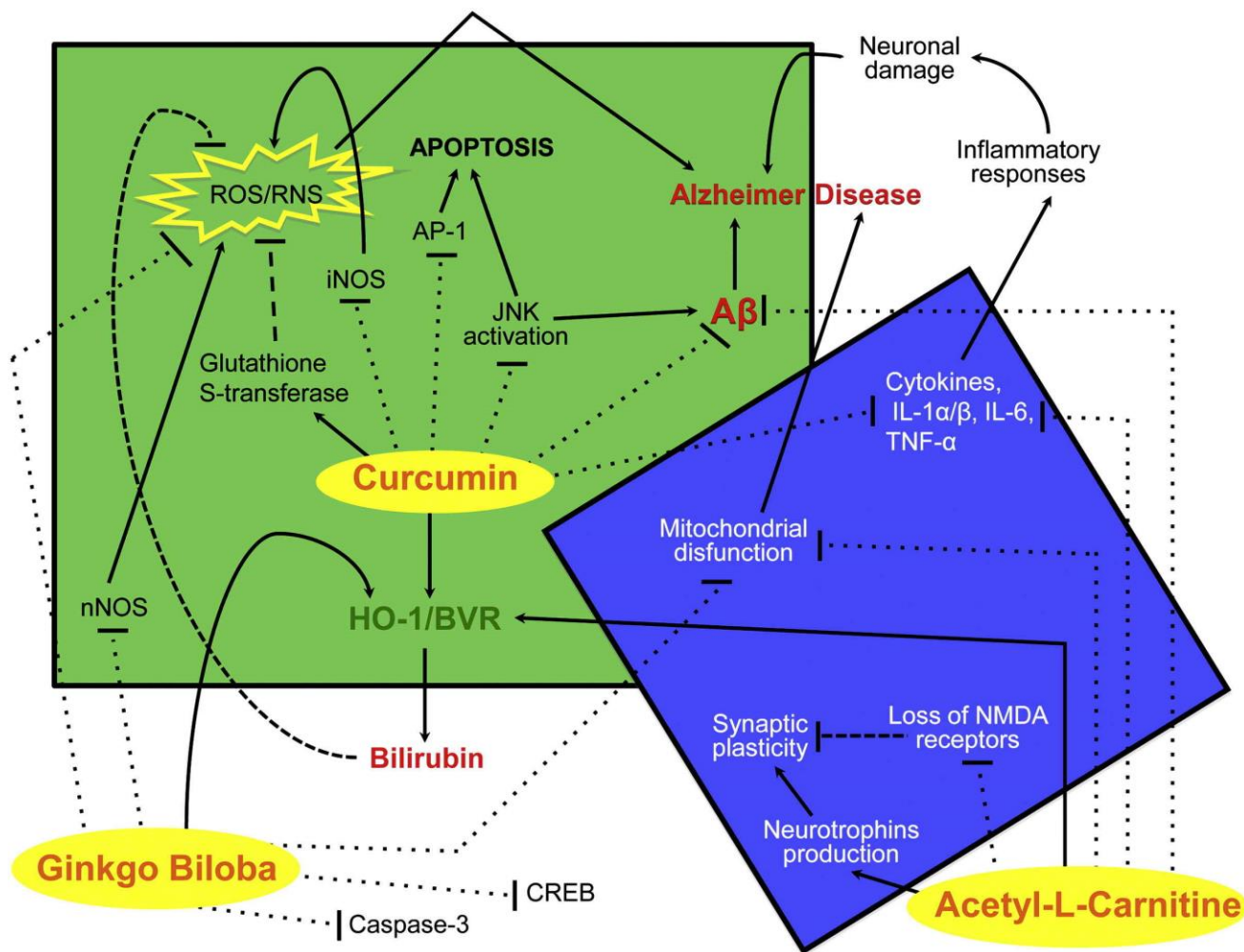
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- ▶ Age-related dementias such as Alzheimer disease (AD) have been linked to **vascular disorders** like hypertension, diabetes and atherosclerosis. These risk factors cause ischemia, inflammation, oxidative damage and consequently reperfusion, which is largely due to **reactive oxygen species (ROS)** that are believed to induce **mitochondrial damage**.
- ▶ At higher concentrations, ROS can cause **cell injury** and **death** which occurs during the aging process, where **oxidative stress** is incremented due to an accelerated generation of ROS and a gradual decline in cellular antioxidant defense mechanisms. **Neuronal mitochondria** are especially vulnerable to oxidative stress due to their role in energy supply and use, causing a cascade of debilitating factors such as the production of giant and/or vulnerable young mitochondrion who's DNA has been compromised.
- ▶ Therefore, **mitochondria specific antioxidants** such as **acetyl-L-carnitine (ALCAR)** and **R- $\alpha$ -lipoic acid (LA)** seem to be potential treatments for AD. They target the factors that damage mitochondria and reverse its effect, thus eliminating the imbalance seen in energy production and amyloid  $\beta$  oxidation and making these antioxidants very powerful alternate strategies for the treatment of AD.

# ALC: effetti neuroprotettivi



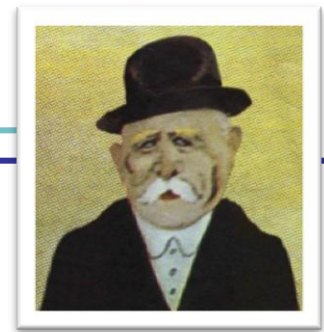
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Mancuso C, Siciliano R, Barone E, et al. Natural substances and Alzheimer's disease: from preclinical studies to evidence based medicine. *Biochim Biophys Acta* 2012; 1822 (5): 616-624



# ALC: effetti neuroprotettivi



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**Table 3**

Some of the main intracellular targets involved in the pharmacological effects of acetyl-L-carnitine.

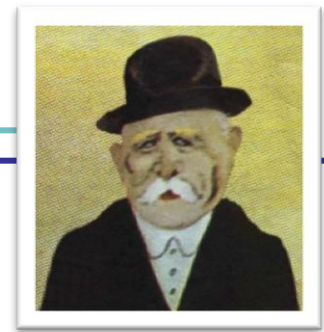
Acetyl-L-carnitine			
Target(s)	Experimental model(s)	Pharmacological effect(s)	Reference(s)
Mitochondria	Rat brain	Improvement of synaptic plasticity	[105,106]
	Rat heart	Stimulation of energy metabolism	
PKC	Rat brain	Amelioration of cognitive function	[108]
NMDA receptors	Rat brain	Amelioration of cognitive function	[111]
NGF	Rat brain	Amelioration of cognitive function	[109,110]
HO-1/BVR Hsp70	Rat brain	Enhancement of the cell stress response	[112,113]

HO-1/BVR, heme oxygenase-1/biliverdin reductase system; NMDA, N-methyl-D-aspartate; NGF, nerve growth factor; PKC, protein kinase C.

# Verso altre indicazioni...

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2013; Early Online: 1–9

**informa**  
healthcare



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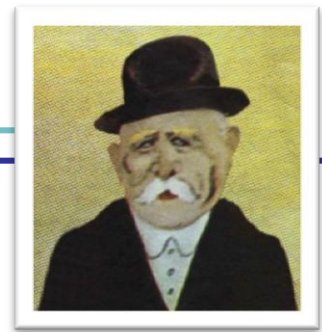
ORIGINAL ARTICLE

## Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS

ETTORE BEGHI<sup>1</sup>, ELISABETTA PUPILLO<sup>1</sup>, VIRGINIO BONITO<sup>2</sup>, PAOLO BUZZI<sup>3</sup>,  
CLAUDIA CAPONNETTO<sup>4</sup>, ADRIANO CHIÒ<sup>5</sup>, MASSIMO CORBO<sup>6</sup>, FABIO GIANNINI<sup>7</sup>,  
MAURIZIO INGHILLERI<sup>8</sup>, VINCENZO LA BELLA<sup>9</sup>, GIANCARLO LOGROSCINO<sup>10</sup>,  
LORENZO LORUSSO<sup>11</sup>, CHRISTIAN LUNETTA<sup>6</sup>, LETIZIA MAZZINI<sup>12</sup>, PAOLO MESSINA<sup>1</sup>,  
GABRIELE MORA<sup>13</sup>, MICHELE PERINI<sup>14</sup>, MARIA LIDIA QUADRELLI<sup>1</sup>,  
VINCENZO SILANI<sup>15</sup>, ISABELLA L. SIMONE<sup>10</sup>, LUCIO TREMOLIZZO<sup>16</sup>  
AND THE ITALIAN ALS STUDY GROUP\*

► Our objective was to assess the effects of **acetyl-L-carnitine (ALC)** with **riluzole** on disability and mortality of amyotrophic lateral sclerosis (ALS). In conclusion, ALC **may be effective**, well-tolerated and safe in ALS. A pivotal phase III trial is needed.

Beghi E, Pupillo E, Bonito V, et al. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2013; 14 (5-6): 397-405



**CEDEM**

**Centro della Memoria**

## **L-acetilcarnitina nelle neuropatie del distretto cervicobrachiale e lombosacrale in pazienti *naive* o *poor responder* a precedente trattamento con acido alfa-lipoico**

*Leonardo Scarzella*

Specialista in Neurologia, Consulente Fondazione Piero Pietro e Giovanni Ferrero, Consulente SOC Neurologia Ospedale di Asti

- ▶ I risultati di questo studio retrospettivo dimostrano che la somministrazione di LAC determina un beneficio significativo sulla **sintomatologia dolorosa neuropatica** di pazienti affetti da cervicobrachialgia o lombosciatalgia.
- ▶ Il miglioramento registrato nei pazienti refrattari a precedente trattamento con AL indica che l'esaltato stress ossidativo è solo una delle molteplici componenti nella patogenesi del dolore neuropatico. In questo contesto la **molteplicità dei meccanismi d'azione della LAC** potrebbe giocare un ruolo decisivo rispetto agli effetti antalgici ed antiinfiammatori convenzionali.

# Concludendo...



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Review

Natural substances and Alzheimer's disease: From preclinical studies to evidence based medicine ☆

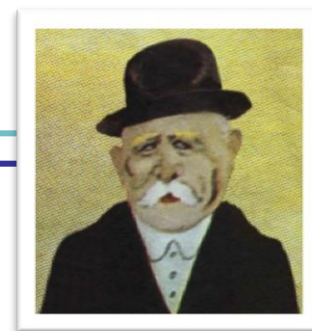
Cesare Mancuso \*, Raffaella Siciliano, Eugenio Barone, Paolo Preziosi

*Institute of Pharmacology, Catholic University School of Medicine, Largo Francesco Vito, 1-00168 Rome, Italy*

- ▶ Despite favorable **pharmacokinetics** (e.g. the ability to cross blood-brain barrier) the lack of therapeutic effect of ALC in AD patients seems to be related to its **pharmacodynamics**.
- ▶ In this frame, the development of new drug-delivery systems which improve systemic bioavailability and brain penetrance and allow the administration of natural substances at low doses has to be considered a **promising strategy**.

Mancuso C, Siciliano R, Barone E, et al. Natural substances and Alzheimer's disease: from preclinical studies to evidence based medicine. *Biochim Biophys Acta* 2012; 1822 (5): 616-624



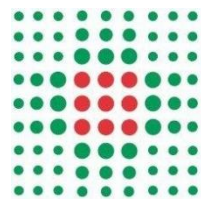


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## Alzheimer's Disease: The Pros and Cons of Pharmaceutical, Nutritional, Botanical, and Stimulatory Therapies, with a Discussion of Treatment Strategies from the Perspective of Patients and Practitioners

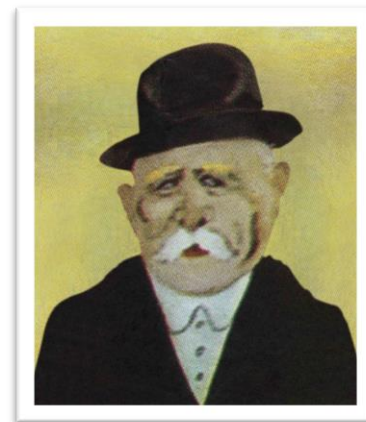
Keith A. Wollen, PhD

- ▶ Although usually the emphasis has been on single-target approaches, AD is characterized by many different cellular dysfunctions, suggesting that a **multi-target approach** may provide more therapeutic value.
- ▶ The goal of this article is to present a current review of pharmaceutical, nutritional, botanical, and stimulatory therapies. **Stimulatory therapies**, which include physical exercise, music, and cognitive training, have received very little attention but may prove to be important adjuncts to more traditional approaches.



SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA  
Azienda Unità Sanitaria Locale della Romagna

U.O. Anziani e Disabili fisici e sensoriali – Rimini



Ferrara, 24 ottobre 2014

## LA “TERAPIA MULTIFATTORIALE” NEL DETERIORAMENTO COGNITIVO DELL’ANZIANO: QUALI EVIDENZE ?

Stefano De Carolis

Responsabile Aziendale del Progetto Demenze per il territorio della Provincia di Rimini

► **L-acetilcarnitina  
e trattamento della  
demenza senile**

***CEDEM***

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