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Dieta e Medical Food nel declino cognitivo lieve
A medical food is in USA defined in 21 U.S.C. as:

A food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognisable scientific principles, are established by medical evaluation.

Medical foods are foods that are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone. They were defined in the Food Drug Administration's and are subject to the general food and safety labeling requirements of the Federal Food Drug and cosmetic act. Medical foods are distinct from the broader category of foods for special dietary use and from traditional foods that bear a health claim. In order to be considered a medical food the product must, at a minimum: be a food for oral ingestion or tube feeding (nasogastric tube); be labeled for the dietary management of a specific medical disorder, disease or condition for which there are distinctive nutritional requirements and be intended to be used under medical supervision.
Federal regulation requires that a product meet all of the following criteria to be considered a medical food.

1. It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube.

2. It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone.

3. The product label specifies that the product is for the dietary management of a medical disorder, disease or condition. It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation.

4. It is intended to be used under medical supervision, and is labeled as such.

5. It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.
Use of medical foods and nutritional approaches in the treatment of Alzheimer’s disease

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SUMMARY

Alzheimer’s disease, the most common cause of dementia, has a high global economic impact. To date, there is no curative treatment; therefore, many efforts are directed not only at novel potential disease-modifying treatments and interventions, but also to develop alternative symptomatic and supportive treatments. Examples of these efforts include the medical foods. There are three medical foods that claim to offer symptomatic benefits: Axona®, Souvenaid® and CerefolinNAC®. Axona supplies ketone bodies as alternative energy source to neurons. Souvenaid provides precursors thought to enhance synaptic function. CerefolinNAC addresses the role of oxidative stress related to memory loss. The current scientific evidence on these medical foods is reviewed in this article. Furthermore, we also review the concept and evidence supporting use of the Mediterranean diet, a possible alternative to medical foods that, if implemented correctly, may have lower costs, fewer side effects and stronger epidemiological health outcomes.

Alzheimer’s disease (AD) is the most common cause of dementia, affecting over 5 million North Americans and 14 million individuals worldwide [1]. In its early stages, AD affects predominantly short-term memory and language ability, with progressive changes in cognitive and functional abilities leading to severe impairments.
Mediterranean diet

The Mediterranean diet does not comprise of medical foods, however, the concept is very similar to medical food whereby a specific healthy dietary pattern is adhered to, which may help in the prevention or delay of AD progression. There are a number of dietary approaches and interventions that have been proposed for the prevention and/or treatment of AD. We included a single dietary approach (i.e., the Mediterranean diet) and its scientific evidence to give one example of possible alternative nutritional approaches that may have lower costs, lower side effects and stronger epidemiologic evidence of health outcomes.

The most common version of the Mediterranean diet was presented by Dr Walter Willett of Harvard University's School of Public Health in the mid-1990s [44]. This diet emphasizes plant-based foods in abundance, fresh fruit as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yogurt), fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts and wine consumed in low to moderate amounts. The total fat in this diet is 25–35% of daily calorie allowance, with saturated fat at 8% or less of daily calorie allowance [44].

A number of published studies found the benefits of adhering to the Mediterranean diet are being less likely to develop depression [45], more than 50% lowering of early death rates [46] and 83% relative reduction in the risk of developing diabetes [47]. The Seven Countries Study report also found the Cretan diet – a type of traditional Mediterranean diet consisting mostly of olive oil, bread, an abundance of fruits and vegetables, fish and moderate amounts of dairy foods and wine – can help lower death rates from heart disease [48]. The Lyon Diet Heart Study was a randomized, controlled trial with free-living subjects. Its goal was to test the effectiveness of a Mediterranean-type diet on the rate of coronary events in people who have had a first heart attack. A total of 302 experimental and 303 control subjects were randomized in the study. The results suggest that a Mediterranean-style diet may help reduce recurrent events in patients with heart disease [49]. The Mediterranean diet is low in
The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

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2.1.1. Concern regarding a change in cognition

There should be evidence of concern about a change in cognition, in comparison with the person’s previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.

2.1.2. Impairment in one or more cognitive domains

There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient’s age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic memory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to a diagnosis of AD dementia. (See the section on the cognitive characteristics later in the text for further details).

2.1.3. Preservation of independence in functional abilities

Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging,
Continuum

- Deficit soggettivo di memoria
- Mild cognitive impairment
- Declino cognitivo

- Lieve
- Lieve moderata
- Moderata
- Moderata grave
- Grave

Figure: Alzheimer's disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)
Efficacy of a medical food in mild Alzheimer’s disease: A randomized, controlled trial

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Abstract

Objective: To investigate the effect of a medical food on cognitive function in people with mild Alzheimer’s disease (AD).

Methods: A total of 225 drug-naïve AD patients participated in this randomized, double-blind controlled trial. Patients were randomized to active product, Souvenaid, or a control drink, taken once-daily for 12 weeks. Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale-revised, and the 13-item modified Alzheimer’s Disease Assessment Scale–cognitive subscale at week 12.

Results: At 12 weeks, significant improvement in the delayed verbal recall task was noted in the active group compared with control ($P = .021$). Modified Alzheimer’s Disease Assessment Scale–cognitive subscale and other outcome scores (e.g., Clinician Interview Based Impression of Change plus Caregiver Input, 12-item Neuropsychiatric Inventory, Alzheimer’s disease Co-operative Study–Activities of Daily Living, Quality of Life in Alzheimer’s Disease) were unchanged. The control group neither deteriorated nor improved. Compliance was excellent (95\%) and the product was well tolerated.

Conclusions: Supplementation with a medical food including phosphatid precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild AD patients. This proof-of-concept study justifies further clinical trials.

Keywords: Alzheimer’s disease; Nutritional intervention; Synapse formation; Membrane phosphatide synthesis; B vitamins; Omega-3 fatty acids; Nucleotides; Uridine; Phospholipids; Choline; Antioxidants; ADAS-cog, delayed verbal recall; Medical food; Dietary management; Randomized clinical trial; Dementia
Efficacy of Souvenaid in Mild Alzheimer’s Disease: Results from a Randomized, Controlled Trial

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6Mettis Cognition Ltd, Kilmington, UK
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Accepted 1 June 2012

Abstract. Souvenaid aims to improve synaptic formation and function. An earlier study in patients with Alzheimer’s disease (AD) showed that Souvenaid increased memory performance after 12 weeks in drug-naive patients with mild AD. The Souvenir II study was a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial to confirm and extend previous findings in drug-naive patients with mild AD. Patients were randomized 1:1 to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. The primary outcome was the memory function domain Z-score of the Neuropsychological Test Battery (NTB) over 24 weeks. Electroencephalography (EEG) measures served as secondary outcomes as marker for synaptic connectivity. Assessments were done at baseline, 12, and 24 weeks. The NTB memory domain Z-score was significantly increased in the active versus the control group over the 24-week intervention period (p = 0.025; Cohen’s d = 0.21; 95% confidence interval [−0.061, 0.49]). A trend for an effect was observed on the NTB total composite Z-score (p = 0.053). EEG measures of functional connectivity in the delta band were significantly different between study groups during 24 weeks in favor of the active group.
Le fasi della malattia di Alzheimer fino alla demenza

Modified from Aisen PS Alzheimers Dement. 2010
La dieta mediterranea: patrimonio culturale dell’umanità dal 2010

Il primo a intuire la connessione tra alimentazione e malattie del ricambio, quali diabete, bulimia, obesità, fu il medico nutrizionista italiano Lorenzo Piroddi (Genova 1911-1999). Considerato il “padre” della dieta mediterranea è anche autore del libro Cucina Mediterranea. Ingredienti, principi dietetici e ricette al sapore di sole. Ancel Keys (1904-2004) si fece promotore dell’ampio programma di ricerca noto come Seven Countries Study e autore del libro Eat well and stay well, the Mediterranean way.
Cultura ed educazione alimentare

Fin dalla prima infanzia a scuola e in famiglia
Dieta mediterranea: ridotto rischio malattie cardiovascolari, diabete e neoplasie maligne.

Quali sono le abitudini alimentari sbagliate?

Un'alimentazione con cibi ricchi di grassi saturi (grassi di origine animale) e di colesterolo aumenta il livello di colesterolo nel sangue, favorendo l'accumulo di questa sostanza sotto forma di placche nella parete stessa dei vasi sanguigni (arterie), che diventano più rigidi: questo processo viene chiamato "aterosclerosi".

Cibi ricchi di grassi saturi o di zuccheri semplici come i dolci apportano nella dieta molte calorie, quasi sempre superiori a quelle necessarie, con conseguente aumento del peso corporeo fino all'obesità. Il sovrappeso e l'obesità, specie se addominale, predispongono al diabete ed aumentano il rischio di malattie cardiovascolari.

Mangiare cibi molto salati favorisce l'aumento della pressione arteriosa, uno dei fattori di rischio più importanti per le malattie cardiovascolari.

L'abitudine di "saltare" i pasti, non mantenendo la giusta cadenza dei 3-5 pasti in cui suddividere l'alimentazione della giornata, favorisce il "senso di fame" e porta a mangiare grandi quantità di cibo in un pasto unico, con conseguente difficile consumo delle calorie introdotte (specialmente se l'unico pasto è quello serale). Tutto ciò facilita l'aumento del peso corporeo e predispone all'obesità.

**PREDIMED Study Investigators:**

Primary prevention of cardiovascular disease with a Mediterranean diet.

AD Risk and combination of nutrients

Observational studies suggest a link between Mediterranean diet & AD risk, but data not fully consistent

**Mediterranean diet:**
- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals

Alcuni riferimenti bibliografici su malattia di Alzheimer e dieta mediterranea e sul ruolo nella conversione da MCI ad AD


- Synaptic proteins and phospholipids are increased in gerbil brain by administering uridine plus docosahexaenoic acid orally. Wutman et al. Brain Res 2006 May 9; 1088 (1): 83-92.


Delay onset of Alzheimer’s disease

Aim for at least 30 minutes of aerobic exercise five times per week. Try walking, swimming, or any other activity that gets your heart rate up. Even routine activities such as gardening, cleaning, or doing laundry count as exercise.

Follow a Mediterranean diet. Eating a heart-healthy Mediterranean diet rich in fish, nuts, whole grains, olive oil, and abundant fresh produce. Treat yourself to the occasional glass of red wine and square of dark chocolate.

Avoid trans fats and saturated fats. Reduce your consumption by avoiding full-fat dairy products, red meat, fast food, fried foods, and packaged and processed foods.

Eat a heart-healthy diet. What’s good for the heart is also good for the brain, so by reducing your risk of heart disease, you also lower your risk of Alzheimer’s disease.
Considerable progress has been made in the past few years in the fight against Alzheimer's disease (AD) and Parkinson's disease (PD). Neuropathological studies in human brains and experimental in vivo and in vitro models support the notion that synapses are affected even at the earliest stages of the neurodegenerative process. The objective of this manuscript is to review some of the mechanisms of synaptic damage in AD and PD. Some lines of evidence support the notion that oligomeric neurotoxic species of amyloid β, α-synuclein, and Tau might contribute to the pathogenesis of synaptic failure at early stages of the diseases. The mechanisms leading to synaptic damage by oligomers might involve dysregulation of glutamate receptors and scaffold molecules that results in alterations in the axonal transport of synaptic vesicles and mitochondria that later on lead to dendritic and spine alterations, axonal dystrophy, and eventually neuronal loss. However, while some studies support a role of oligomers, there is an ongoing debate as to the exact nature of the toxic species. Given the efforts toward earlier clinical and preclinical diagnosis of these disorders, understanding the molecular and cellular mechanisms of synaptic degeneration is crucial toward developing specific biomarkers and new therapies targeting the synaptic apparatus of vulnerable neurons.
Synapse loss is structural basis of deficits in people with AD – Our lead for intervention target

Physical Basis of Cognitive Alterations in Alzheimer’s Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,⁎ Elierer Masliah, MD,⁎ David P. Salmon, PhD,⁎ Nelson Butters, PhD,‡ Richard DeTeresa, BS,⁎ Robert Hill, PhD,⁎ Lawrence A. Hansen, MD,⁎ and Robert Katzman, MD⁎


Reduced number of synapses

VIEWPOINT

Alzheimer’s Disease Is a Synaptic Failure

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002
A Nutrient Combination that Can Affect Synapse Formation

Richard J. Wurtman

*Nutrients 2014, 6, 1701-1710*

All cells utilize DHA and other fatty acids (e.g., EPA); uridine; and choline to form the phosphatide compounds that constitute the major components of their membranes. PC, the most abundant phosphatide in brain, is synthesized from these precursor-nutrients by a set of enzymes that comprise the CDP-choline cycle (or “Kennedy Cycle”). This biochemical pathway also generates a related is formed from PC. Thus, all of the principal lipid components of synaptic membranes are affected by the rate at which PC is being formed. In addition, since each of the reactions needed to convert choline, uridine, and DHA to PC is catalyzed by a low-affinity enzyme, blood levels of the three nutrient-precursors can determine not only PC’s rate of synthesis but also the rates at which almost all of the brain’s membrane lipids are produced. When all three of the nutrients are provided concurrently the resulting increase in PC production is greater than the sum of the increases produced by giving each separately [1,2]. This probably occurs because if just one of the nutrient-precursors were to be provided, the concentrations of the other two would continue to be limiting.
Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis neuronal membrane

Phospholipids are main constituents of synapses

Kennedy pathway is dependent on a supply of precursors from the circulation
B vitamins as cofactor needed for endogenous production of membrane precursors

PEMT = phosphatidylethanolamine -N-methyltransferase
Development of Souvenaid
Contains the investigated key nutrients

HYPOTHESIS:
Souvenaid successfully addresses an unmet nutritional need in people with AD by increasing their intake of these dietary precursors and co-factors:

- Uridine (UMP)
- Omega-3 fatty acids
- Phospholipids
- Choline
- B-Vitamins
- Antioxidants
5-year observational study, with 525 community-dwelling participants enrolled, aged 70 and older and otherwise healthy.
Commentary

A Nutritional Approach to Ameliorate Altered Phospholipid Metabolism in Alzheimer’s Disease

We previously tested, in drug-naïve patients with very mild to mild AD [8], the nutritional intervention Souvenaid® (125 mL, taken once daily) containing the specific nutrient combination Fortasyn® Connect in a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial. In the present study, some baseline and 24-week plasma samples, chosen at random, of subjects taking either the investigational product (n=47) or a control product (n=49) were analysed for lipid profiles at the Kansas Lipidomics Research Center using electrospray ionization tandem mass spectrometry.

Our findings suggest that a nutritional intervention that raises levels of nutrients normally rate-limiting in phospholipid synthesis may also be useful in asymptomatic subjects with plasma lipid biomarker profiles predictive for phenoconversion to aMCI/AD.
**Single nutrient interventions in AD/MCI: in general no beneficial effects on cognition**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Author</th>
<th>Journal</th>
<th>#Subjects/Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>n3 PUFAs</td>
<td>Quinn 2010</td>
<td>JAMA</td>
<td>402/18 months</td>
<td>DHA compared with placebo did not slow the rate of cognitive and functional decline in mild-moderate AD patients.</td>
</tr>
<tr>
<td></td>
<td>Freund-Levi 2006</td>
<td>Arch Neurol</td>
<td>174/6 months</td>
<td>Administration of n3PUFA in mild-moderate AD patients did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the ADAS. However, positive effects were observed in a small group of patients with very mild AD (MMSE&gt;27)</td>
</tr>
<tr>
<td>B-vitamins</td>
<td>Aisen 2008</td>
<td>JAMA</td>
<td>409/18 months</td>
<td>This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.</td>
</tr>
<tr>
<td></td>
<td>McMahon 2006</td>
<td>N Eng J Med</td>
<td>276/24 months</td>
<td>The results of this trial do not support the hypothesis that homocysteine lowering with B vitamins improves cognitive performance.</td>
</tr>
<tr>
<td>Vitamin E / Antioxidants</td>
<td>Dysken 2014</td>
<td>JAMA</td>
<td>304/mean f-up 27 months</td>
<td>Among patients with mild to moderate AD, 2000 IU/d of alpha-tocopherol compared with placebo resulted in slower functional decline.</td>
</tr>
<tr>
<td></td>
<td>Petersen 2005</td>
<td>N Eng J Med</td>
<td>769/36 months</td>
<td>Vitamin E had no benefit in patients with mild cognitive impairment.</td>
</tr>
<tr>
<td></td>
<td>Galasko 2012</td>
<td>Arch Neurol</td>
<td>52/16 weeks</td>
<td>However, this treatment (vitamin E + vitamin C plus α-lipoic acid) raised the caution of faster cognitive decline</td>
</tr>
<tr>
<td>Vitamin D2</td>
<td>Stein 2011</td>
<td>J Alz Disease</td>
<td>32/8 weeks</td>
<td>We conclude that high-dose vitamin D provides no benefit for cognition or disability over low-dose vitamin D in mild-moderate AD</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>DeKosky 2008</td>
<td>JAMA</td>
<td>3069/median f-up 6.1 Y</td>
<td>Ginkgo biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.</td>
</tr>
</tbody>
</table>
Vitamin E had no benefit in patients with mild cognitive impairment.

Long-term use of vitamin E supplements did not provide cognitive benefits among generally healthy older women.
Development of Fortasyn connect
Targeted to improve formation of synapses

- **Uridine (UMP)**: 625 mg
- **Omega-3 fatty acids**: EPA 1200 mg, DHA 300 mg
- **Choline**: 400 mg
- **Phospholipids**: 106 mg
- **B vitamins**: folic acid 400 mcg, Vit B6 1 mg, Vit B12 3 mcg
- **Antioxidants**: Vit C 80 mg, Vit E 40 mg, Selenium 60 mcg

Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands), a Food for Special Medical Purposes (FSMP), has undergone an extensive, 12-year development programme. It has been designed to address the specific nutritional needs of patients with early Alzheimer’s disease, the stage when there are still abundant functional synapses and intervention may be most effective. By targeting rate-limiting steps of the Kennedy pathway, Souvenaid® aims to increase synaptic membrane formation. Souvenaid® is a 125 mL, multi-nutrient drink to be

(Table 1) (34). These nutrients are present in Souvenaid® at levels above those that can be achieved in the normal diet, and the aim of Souvenaid® is to rectify nutritional deficiencies that may limit synaptogenesis.
Key phenomena being studied

- Increase precursor supply
- Increase phosphatide / membrane synthesis
- Increase neurite outgrowth
- Increase synapses
- Increase neurotransmission (ACh synthesis, release, receptors)
- Synergy between nutrients
- Improve learning
- Complete mixture (learning and memory, synapse)

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11. de Wilde et al. (2003) Brain Res
12. de Wilde et al. (2002) Brain Res
13. de Bruin et al. (2003) J Learn Mem
15. De Wilde et al. (2011) J Alz Dis
La terapia farmacologica della malattia di Alzheimer:
È multimodale (cioè rivolta sia al controllo dei sintomi cognitivi che comportamentali), si avvale degli inibitori delle colinesterasi, indicati e rimborsati in fase lieve-moderata (MMSE 26-10) e della memantina, indicata in fase moderata severa, rimborsata in fase moderata (MMSE 20-10).
1. Antonino Cotroneo (Torino),
2. Innocenzo Rainero (Torino),
3. Domenica La Milia (San Maurizio Canavese),
4. Loredana Seccia (Omegna),
5. Roberto Confalonieri (Monza),
6. Fabiola Teruzzi (Monza),
7. Daniele Perotta (Rho),
8. Manuela Teresa Mazzà (Milano),
9. Massimo Moleri (Bergamo),
10. Angelo Bianchetti (Brescia),
11. Simona Gentile (Cremona),
12. Annachiara Bonazzi (Verona),
13. Laura De Togni (Verona),
14. Giuseppe Gambina (Verona),
15. Carlo Gabelli (Padova),
16. Flavio Cursi (Roma),
17. Stefano Ronzoni (Roma),
18. Maria Carmela Lechìara (Avezzano),
19. Antonio Lera (Giulianova),
20. Nicola Serroni (Teramo),
21. Francesco Di Blasio (Teramo),
22. Gina Varricchio (Caserta),
23. Francesco Fiorillo (San Cipriano D’Aversa),
24. Carmine Fuschillo (Saviano),
25. Patrizia Bruno (Napoli),
26. Vincenzo Canonico (Napoli),
27. Anna Maria Papantonio (Foggia),
Preliminary results from a caregiver survey

- Objective to assess the impact of Souvenaid on patients with cognitive impairment in a ‘real-world’ setting
- Total number of patients: 387 (female: 60%) recruited in 30 AD clinics in Italy
- Age: 75.9y (+/- 7.2), range 50-99y
- Open label observation survey in patients taking Souvenaid for a mean of 3.6 months (range 1-12)

**Diagnosis**

- MCI: 33.1%
- AD: 47.7%
- Other Dementia: 8.3%
- Other: 9.3%
- Depression: 1.7%

**Other medications**

- Achei: 27.6%
- Memantine: 13.9%
- Nootropics: 5.9%
- Antidepressants: 29.9%
Distribuzione del campione in relazione ai valori di MMSE alla baseline

Il MMSE basale medio dell’intero campione era $21,0 \pm 4,97$. 
Tollerabilità

- Soltanto in 20 casi (6.5% del campione) si sono presentati problemi di tolleranza al trattamento.
- Il 24.0% dei soggetti ha riferito difficoltà legate al costo del trattamento.

- Compliance Souvenir II (24 w) 96.6% nei controlli e 97.1% nei trattati (Scheltens et al, J Alzheimers Dis. 2012)
- OLE a 1 anno 83% in trattamento (Olde Rikkert et al. In press)
Methods and analysis

- Interview of patients and caregivers at the follow-up visit after taking Souvenaid for at least three months
- A structured interview was used to explore the modification of cognitive, behavioral and functional domains in a ‘real life’ situation

<table>
<thead>
<tr>
<th>Domain</th>
<th>Caregiver interview</th>
<th>Patient interview</th>
</tr>
</thead>
</table>
| Behaviour | 1. apathy/interest  
            2. agitation/irritability  
            3. sleep  
            4. eating behavior | 1. depression complain |
| Function | 1. household activities/hobbies  
              2. outdoor activities  
              3. books/newspaper reading | 1. household activities/hobbies |
| Cognition | 1. remember appointments commitments dates  
                      2. identify persons/remember names  
                      3. orientation in new place | 1. subjective memory  
                                      2. orientation in and out home |

The answers were standardized using a hierarchical scale:
- 1: worsened, 2: slightly worsened, 3: unchanged, 4: slightly improved, 5: improved
- A single domain score and a global score were calculated for the analysis
RISPETTO ALLA PRESTAZIONI COGNITIVE

11. Ricordare appuntamenti/impegni/date: rispetto alla capacità di ricordare gli appuntamenti, gli impegni, ai comportamenti ripetitivi (chiedere più volte le stesse cose) lei ritiene che la situazione attuale sia

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata

12. Riconoscere/ricordare nomi di persone: rispetto alla capacità di riconoscere le persone che incontra (familiari, amici, conoscenti) e ricordarne i nomi ritiene che la situazione attuale sia

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata

13. Orientarsi in ambienti nuovi: rispetto alla capacità di orientarsi in ambienti nuovi (come centri commerciali, ristoranti, hotel, case di amici/conoscenti) ritiene che la situazione attuale sia

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata

RELATIVAMENTE AGLI EFFETTI DEL TRATTAMENTO CON SOUVENAIR, QUALI IMPRESSIONI DI EFFICACIA HA AVUTO IL PAZIENTE STESSO?
(le risposte vanno ottenute attraverso il colloquio clinico diretto al paziente quando lo stesso è in grado di rispondere; il giudizio soggettivo deve essere poi strutturato come indicato)

14. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi della memoria (difficoltà a ricordare le date, gli appuntamenti, necessità di chiedere più volte le cose oggi si sente

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata

15. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi di orientamento (difficoltà a orientarsi fuori casa, quando va a trovare amici o parenti, quando visita un luogo nuovo oggi si sente

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata

16. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi nello svolgere le attività usuali (la gestione della casa, cucinare, fare la spesa, occuparsi dei suoi hobby) oggi si sente

☐ decisamente peggiorata  ☐ lievemente peggiorata  ☐ sostanzialmente invariata
☐ lievemente migliorata  ☐ decisamente migliorata
Descrizione dei giudizi di efficacia dei caregiver nella popolazione generale rispetto agli item considerati.

Dal 27 al 47% dei caregiver fornisce un giudizio positivo sull’efficacia del trattamento (lievemente/decisamente migliorato); l’apatia e la memoria circa gli appuntamenti sono le variabili che risultano migliorate con frequenza più elevata; l’orientamento e il comportamento alimentare mostrano i miglioramenti meno rilevanti.
Descrizione dei giudizi di efficacia dei pazienti nella popolazione generale rispetto agli item considerati.

Il giudizio dei pazienti è positivo dal 36 al 43% dei casi (massimo per la memoria, minimo per orientamento e attività).
Confronto fra i giudizi di efficacia espressi dai caregiver dei pazienti con AD rispetto a quelli con MCI per gli item considerati (i dati rappresentano le percentuali).

Sono risultate statisticamente significative (test chi-square) le differenze per gli item “memoria per appuntamenti” (p=0.04) e “orientamento” (p=0.02).
Confronto fra i giudizi di efficacia espressi *dai pazienti* con AD rispetto a quelli con MCI per gli item considerati (i dati rappresentano le percentuali).
Sono risultate statisticamente significative (test chi-square) le differenze per gli item “orientamento” (p=0.06)
La risposta al trattamento si correla in modo significativo con la durata del trattamento ($r=0.115; p=.05$; fig A) e con i valori del MMSE alla baseline ($r=.229; p=.0001$).

**Fig A**

**Fig B**
Dalle sperimentazioni al real world due casi clinici

AP:

Paziente 1, donna, 80 aa, sco 5 aa

AP: IPA, ateromasia carotidea, insufficienza venosa cronica.

DIAGNOSI DI MCI amnesico 06/06/2013 c/o ns centro.

13/09/2013 T0 MMSE 25/30 Clock 8/10. Start Souvenaid.

19/03/2014 T6 MMSE 28/30 Clock 9/10

Caregiver: “da quando assume Souvenaid è sensibilmente migliorata l’abulia, l’apatia e l’aggressività verbale; è più partecipe e più collaborativa.”

24/09/2014 T12 MMSE 26/30 Clock: 9/10

Caregiver: “Non è peggiorata la memoria, rimane attiva e partecipe anche se in alcuni momenti sembra più persa.”

Nel periodo di osservazione non sono accaduti eventi clinici rilevanti e la paziente non ha modificato la terapia farmacologica assunta a TO.
Arrivederci a Milano