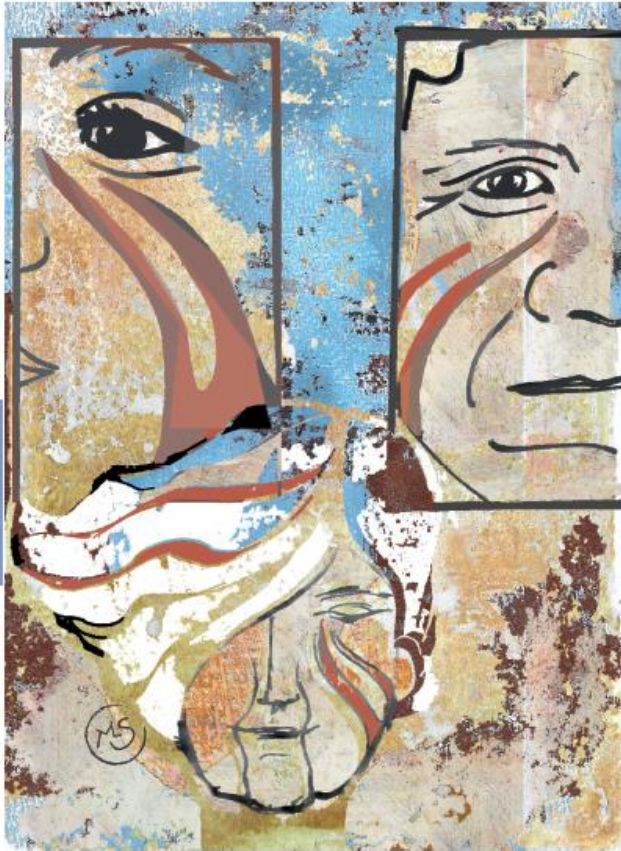


LIBERI E LONGEVI



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SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Università degli
Studi di Napoli
Federico II
Polo Didattico
di **SCAMPIA**

Ruolo dei “vecchi” farmaci per i disturbi cognitivo-comportamentali

Angelo Bianchetti

Responsabile Dipartimento di Riabilitazione Neuro-Fisiatrice e Neuro-Geriatria
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Società Italiana di Gerontologia e Geriatria
Associazione Italiana di Psicogeriatria

Conditions presenting with significant cognitive decline in the elderly

Condition/Category	Category Type	Typical Onset & Progression	Key Distinguishing Features in the Elderly
Major Neurocognitive Disorder (Dementia)	Progressive/Chronic NCD	Insidious and gradual decline, becoming steadily worse over years.	Significant cognitive decline that interferes with independence in daily activities (ADLs/IADLs).
Mild Neurocognitive Disorder (Mild NCD / MCI)	Progressive/Chronic NCD	Gradual decline, slower than Major NCD.	Modest cognitive decline that does not interfere with independence in complex daily activities. May progress to Major NCD.
Depression	Psychiatric Mimic	Can be rapid or subacute.	Presents as difficulty concentrating, apathy, and memory complaints (pseudodementia). Symptoms often improve significantly with mood treatment.
Delirium	Acute NCD	Acute (hours to days) onset; attention and awareness fluctuate .	Severe, short-term confusion, often caused by an acute medical issue (e.g., infection, drug reaction).
Structural Brain Issues	Potentially Reversible/Stable	Onset can be sudden (TBI, hemorrhage) or insidious (NPH, tumor).	Includes conditions like Subdural Hematoma, Brain Tumors, or NPH .
Medication Side Effects/Toxicity	Reversible/Substance-Related	Can be acute or gradual, depending on medication.	Cognitive impairment (especially confusion, memory issues) related to timing of new prescriptions or combinations of drugs (e.g., anticholinergics).
Nutritional Deficiencies/Metabolic Endocrine Issues	Reversible/Metabolic	Gradual onset.	Deficiencies in vitamins like B12 or thyroid dysfunctions, or imbalances in sodium or calcium can cause significant cognitive and neurological impairment.

based on DSM 5 definition

Cognitive disorders

All conditions that can cause cognitive impairment. These include neurodegenerative conditions such as Alzheimer's disease, but also vascular disease, traumatic brain injury, substance use, infections, disturbances of cerebrospinal fluid dynamics, psychiatric conditions, secondary or reversible cognitive disorders, and more.

DSM-5 refers to "neurocognitive disorders" to differentiate the cognitive impairment of psychoses.

We believe that the "neuro" prefix does not add meaningful information as, by definition, the brain is the organ responsible for all cognitive disorders.

What is **Alzheimer's disease**? Depending on who is asked, the answers vary, even among doctors and specialists. The definition of Alzheimer's disease is in dynamic evolution in the expert community, and unanimity has not yet been reached. For all practical purposes, Alzheimer's disease in clinical practice consists of cognitive impairment associated with biomarker evidence of its neuropathological hallmarks: β -amyloid plaques composed of aggregated β -amyloid, and neurofibrillary tangles composed of aggregated tau.

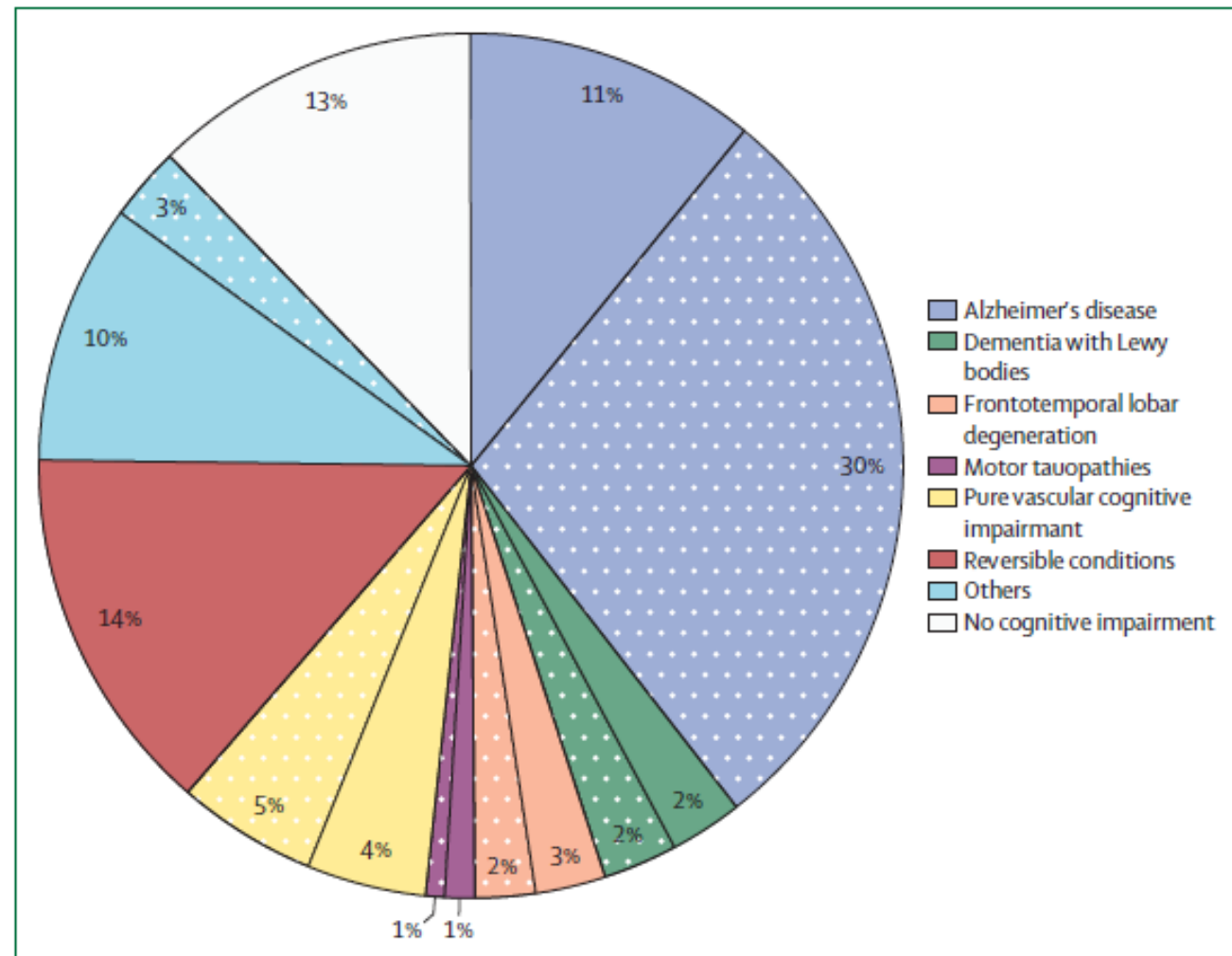


Figure 3: Taxonomy of patients and use of diagnostic biomarkers at selected memory clinics

For each colour, cases diagnosed with (dotted) and without (non-dotted) cerebrospinal fluid or PET biomarkers are shown. Based on a survey of 16 526 new consecutive diagnostic patients consulted from Jan 1, 2022, to Dec 31, 2023, in the memory clinics of Amsterdam, Cologne, Copenhagen, Geneva, Lund, Munich, and Paris. Reversible conditions include normal pressure hydrocephalus, meningioma, metabolic conditions, depression. Other section includes low achievement, psychiatric conditions, unsuccessful brain ageing. No cognitive impairment includes subjective cognitive decline, functional cognitive and other psychiatric disorders, neurologic diseases, physical comorbidity, somatic comorbidity, polypharmacy. More details in appendix (pp 10–11).

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Volume 327

OCTOBER 29, 1992

Number 18

A DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY OF TACRINE FOR ALZHEIMER'S DISEASE

KENNETH L. DAVIS, M.D., LEON J. THAL, M.D., ELKAN R. GAMZU, PH.D., CHARLES S. DAVIS, PH.D., ROBERT F. WOOLSON, PH.D., STEPHEN I. GRACON, PH.D., DAVID A. DRACHMAN, M.D., LON S. SCHNEIDER, M.D., PETER J. WHITEHOUSE, M.D., PH.D., TONI M. HOOVER, PH.D., JOHN C. MORRIS, M.D., CLAUDIA H. KAWAS, M.D., DAVID S. KNOPMAN, M.D., NANCY L. EARL, M.D., VINOD KUMAR, M.D., RACHELLE S. DODDY, M.D., AND THE TACRINE COLLABORATIVE STUDY GROUP*

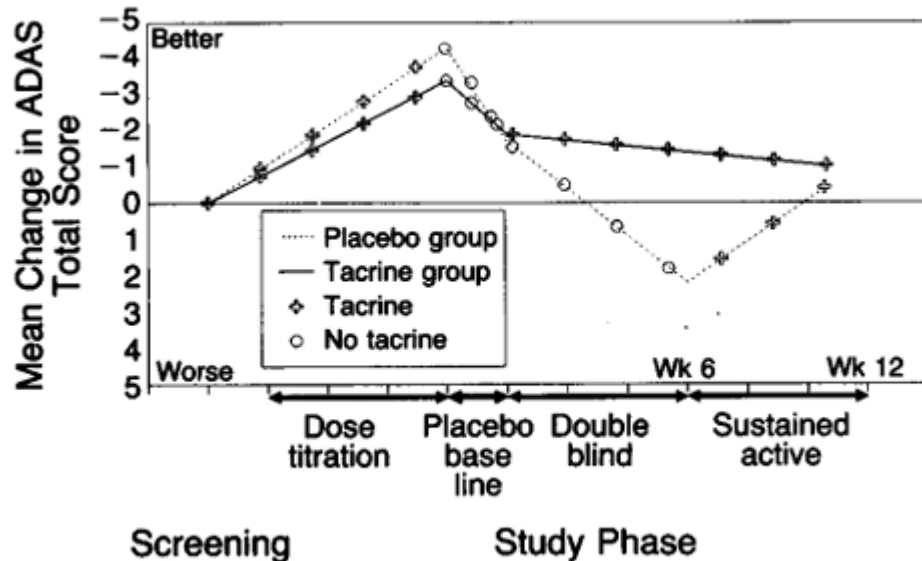


Figure 2. Mean Change in ADAS Total Score during the Phases of the Study.

FDA NEWS RELEASE

FDA Grants Accelerated Approval for Alzheimer's Drug

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For Immediate Release: June 07, 2021

Today, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. Aduhelm was approved using the [accelerated approval pathway](#), which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit.

"Alzheimer's disease is a devastating illness that can have a profound impact on the lives of people diagnosed with the disease as well as their loved ones," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "Currently available therapies only treat symptoms of the disease; this treatment option is the first therapy to target and affect the underlying disease process of Alzheimer's. As we have learned from the fight against cancer, the accelerated approval pathway can bring therapies to patients faster while spurring more research and innovation."

J Prev Alz Dis 2022;2(9):197-210
Published online March 18, 2022, <http://dx.doi.org/10.14283/jpad.2022.30>

Original Research

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Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

S. Budd Haeberlein¹, P.S. Aisen², F. Barkhof^{3,4}, S. Chalkias^{1,5}, T. Chen¹, S. Cohen⁵, G. Dent¹, O. Hansson^{6,7},

EMERGE and ENGAGE were halted based on [futility analysis](#) of data pooled from the first approximately 50% of enrolled patients; subsequent efficacy analyses included data from a larger data set collected up to futility declaration and followed prespecified statistical analyses.

The primary endpoint was met in EMERGE (difference of -0.39 for high-dose aducanumab vs placebo [95% CI, -0.69 to -0.09; P=.012; 22% decrease]) but not in ENGAGE (difference of 0.03, [95% CI, -0.26 to 0.33; P=.833; 2% increase]).

[Results of biomarker substudies confirmed target engagement and dose-dependent reduction in markers of Alzheimer's disease pathophysiology.](#)

The most common adverse event was amyloid-related imaging abnormalities-edema.

Treats cognitive symptoms (memory and thinking)

Name (Generic/Brand)	Indicated For	Common Side Effects
Donepezil Aricept®	Mild to severe dementia due to Alzheimer's	Nausea, vomiting, loss of appetite, muscle cramps and increased frequency of bowel movements.
Galantamine Razadyne®	Mild to moderate dementia due to Alzheimer's	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Rivastigmine Exelon®	Mild to moderate dementia due to Alzheimer's or Parkinson's	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Memantine Namenda®	Moderate to severe dementia due to Alzheimer's	Headache, constipation, confusion and dizziness.
Memantine + Donepezil Namzaric®	Moderate to severe dementia due to Alzheimer's	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

Change disease progression

Name (Generic/Brand)	Indicated For	Common Side Effects
Donanemab Kisunla™	Alzheimer's disease (MCI or mild dementia)	ARIA and headache
Lecanemab Leqembi®	Alzheimer's disease (MCI or mild dementia)	Infusion-related reactions, ARIA and headache

Treats non-cognitive symptoms (behavioral and psychological)

Name (Generic/Brand)	Indicated For	Common Side Effects
Brexpiprazole Rexulti®	Agitation associated with dementia due to Alzheimer's disease	Weight gain, sleepiness, dizziness, common cold symptoms, and restlessness or feeling like you need to move. Warning for serious side effects: increased risk of death in older adults with dementia-related psychosis. Rexulti is not approved for the treatment of people with dementia-related psychosis without agitation that may happen with dementia due to Alzheimer's disease.
Suvorexant Belsomra®	Insomnia, has been shown to be effective in people living with mild to moderate Alzheimer's disease	Impaired alertness and motor coordination, worsening of depression or suicidal thinking, complex sleep behaviors, sleep paralysis, compromised respiratory function.

La fase stessa della diagnosi è premessa indispensabile all'atto terapeutico, divenendo l'inizio di un intenso rapporto fra il medico, il paziente e la sua famiglia, nel quale esistono ampi stazi di intervento.

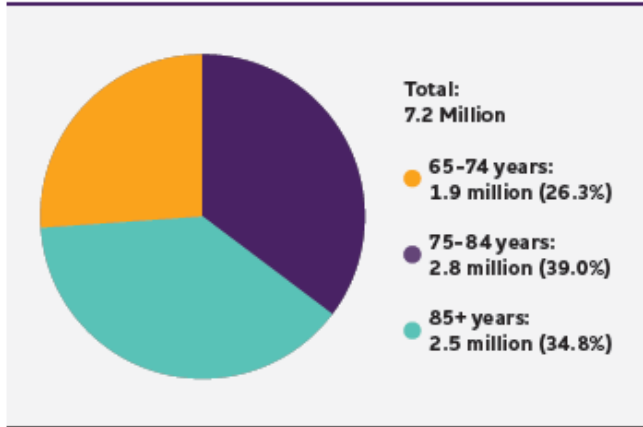
Bianchetti A e Trabucchi M, 2003

Treatment (management) of dementia (in elderly)

- Lifestyle modifications (*physical activity, nutrition, social network, etc*)
- Assessment and management of frailty
- Treatment of somatic diseases (*avoiding overmedication*)
- Specific pharmacological treatment
- NPS treatments (pharmacological and not pharmacological)
- Rehabilitation and physical, cognitive and behavioural stimulations
- Patients' and caregivers' education and support
- Socio-economic interventions, institutionalization
- Ethical decisions

2025 ALZHEIMER'S DISEASE FACTS AND FIGURES

Number and Ages of People 65 or Older with Alzheimer's Dementia, 2025*

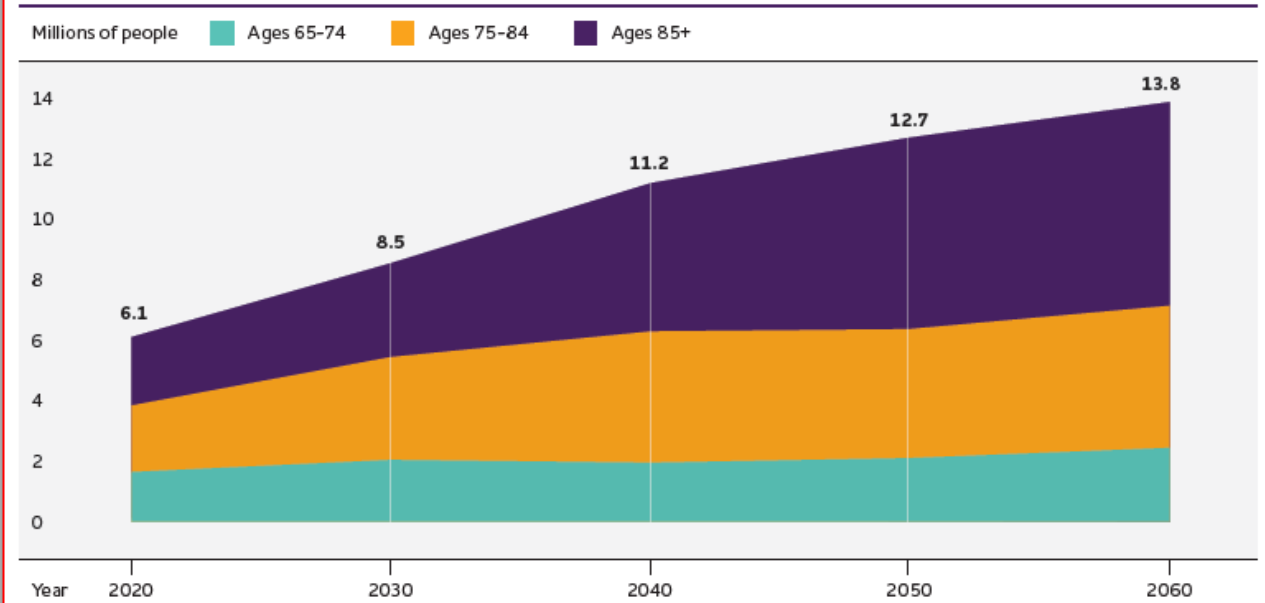


*Percentages do not total 100 due to rounding.

Created from data from Rajan et al.^{A2, 293}

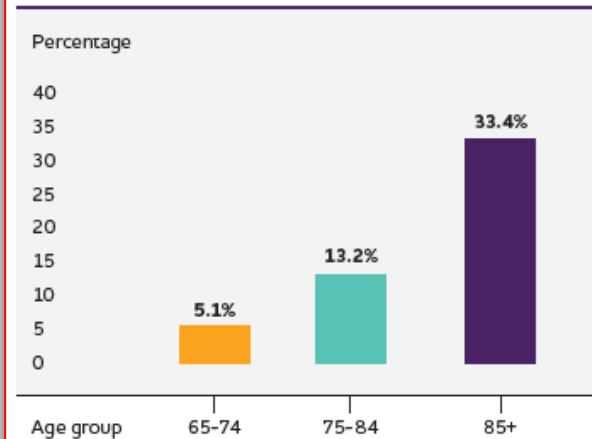
The denominator for each percentage is the total number of people with Alzheimer's dementia in the U.S. in 2025: 7.2 million.

Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060



Created from data from Rajan et al.^{A5, 293}

Percentage of People with Alzheimer's Dementia by Age Group, 2025



*Percentages do not total 100 due to rounding.

Created from data from Rajan et al.^{A2, 293}

The denominator for each percentage is the U.S. Census population projection for the specific age group of interest.

Età media pazienti con demenza ATS Brescia 84 anni (dati Dr Sileo)

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

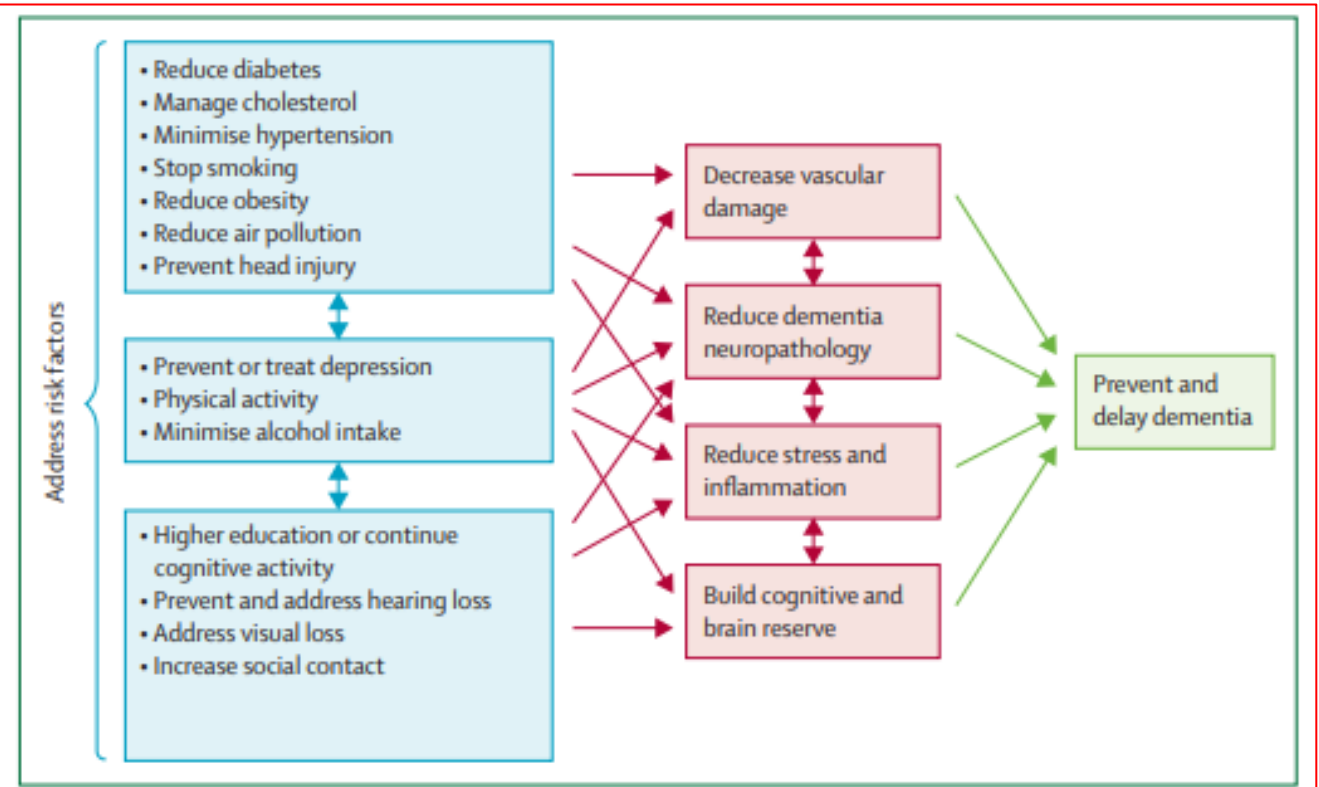
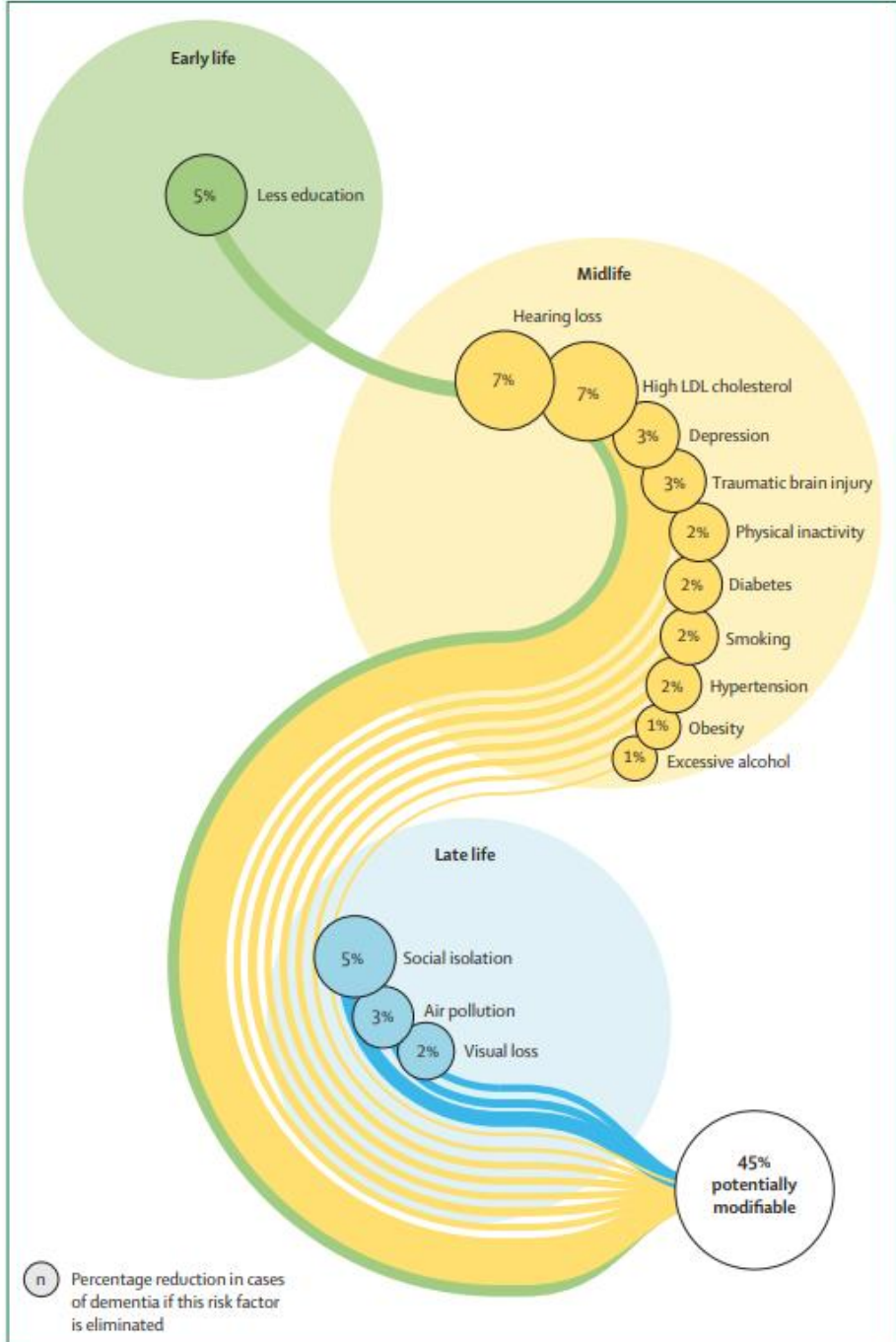


Figure 2: Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia



n Percentage reduction in cases of dementia if this risk factor is eliminated

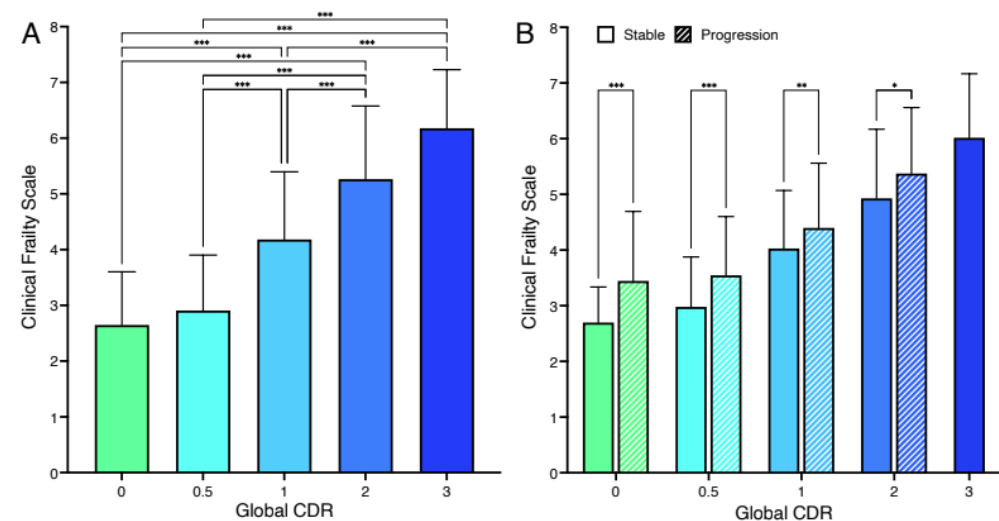
Figure 9: Population attributable fraction of potentially modifiable risk factors for dementia

Defining the Role of Frailty in the Transition from Mild Cognitive Impairment to Dementia and in Dementia Progression

Alberto Benussi ^{1 2}, Irene Mattioli ³, Chiara Silvestri ¹, Ilenia Libri ¹, Silvio Zampini ¹, Maura Cosseddu ², Rosanna Turrone ², Claudia Amolini ^{4 5}, Salvatore Caratozzolo ², Barbara Borroni ^{1 2}, Alessandra Marengoni ^{4 5}, Alessandro Padovani ^{1 2}

Results: Frailty significantly increased with higher global clinical dementia rating (CDR) subgroups, suggesting escalating frailty burden with disease progression. Age, CFS, and mini-mental state examination (MMSE) scores were significant predictors of progression from MCI to dementia and to more severe dementia stages, even when considering the independence from variables contributing to frailty. Patients transitioning to a higher CDR group exhibited higher CFS scores. Age, education, anticholinergic burden, cumulative illness rating scale - geriatric, MMSE, and neuropsychiatric inventory scores significantly contributed to frailty.

Conclusions: Frailty plays a critical role in the transition from MCI to dementia and within dementia progression. Age, cognitive impairment, and frailty were identified as significant predictors of disease progression. The CFS is a clinically applicable tool for frailty assessment. Regular frailty assessments may be valuable in early detection and management of dementia.

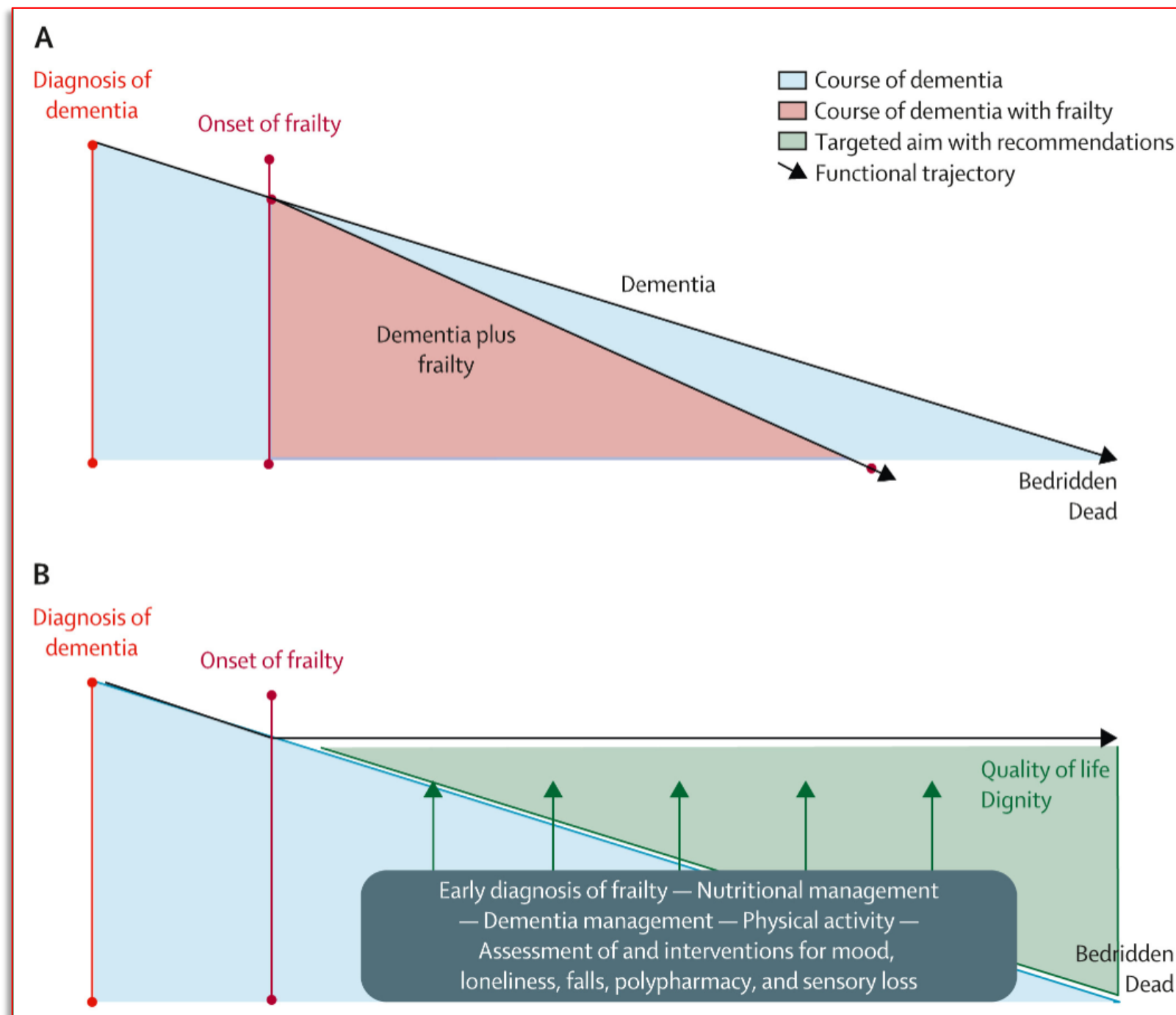


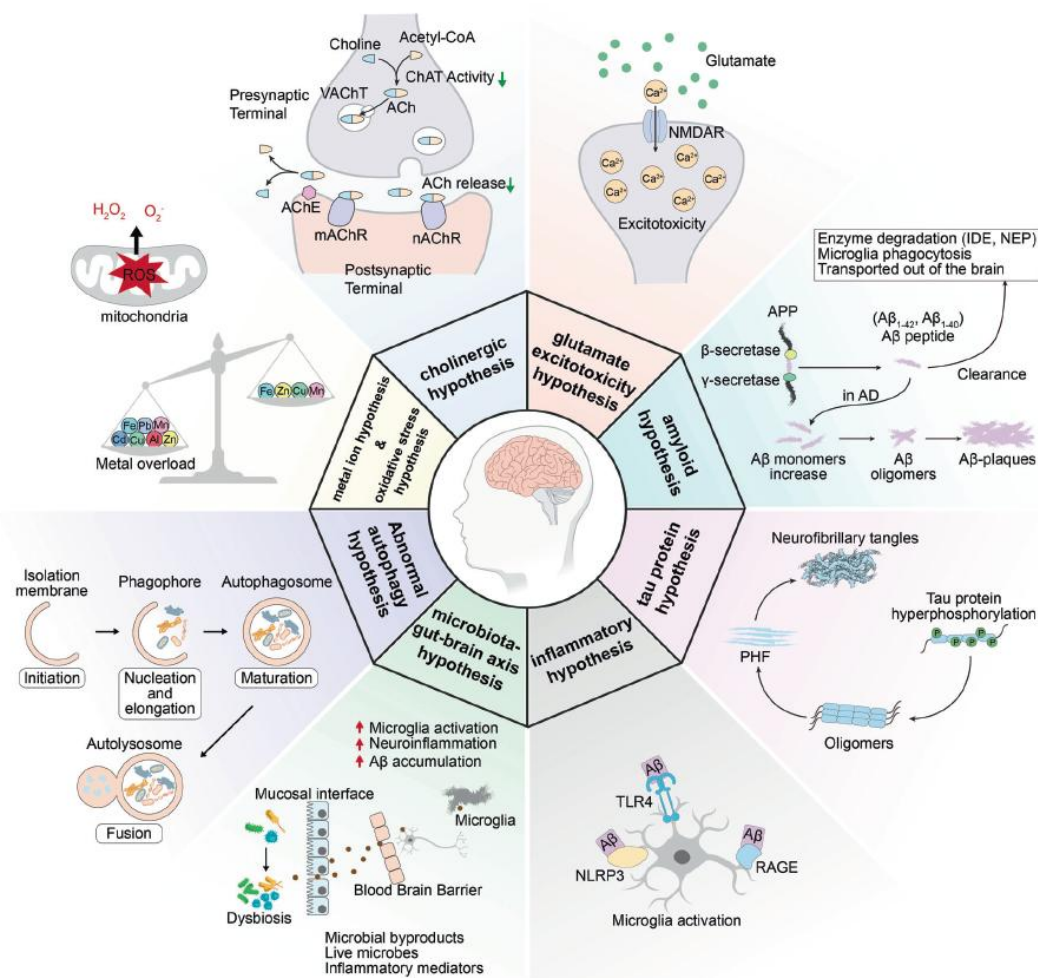


Lancet Healthy Longev 2025;
6: 100666

Assessment and management of frailty in individuals living with dementia: expert recommendations for clinical practice

(A) Functional prognosis of a person with dementia alone or with dementia and frailty. (B) The aim of the comprehensive interventions referred to in the recommendations. Another common scenario exists in which frailty precedes the onset of dementia but exhibits the same synergistic negative effect.





The glutamatergic excitotoxicity hypothesis

Excessive stimulation of NMDA receptors by glutamate leads to neuronal damage in AD due to increased calcium influx, which triggers various harmful processes, including the generation of reactive oxygen species and mitochondrial dysfunction. This overstimulation results in neuronal swelling and ultimately causes permanent excitotoxic damage, contributing to cognitive decline .

Amyloid hypothesis

The accumulation of Aβ is a hallmark pathological feature in both extensively studied autosomal dominant AD and sporadic late- onset AD patients. Aβ originates from the processing of the APP, a transmembrane glycoprotein, through its sequential cleavage by β-secretase and γ-secretase (a multiprotein complex with PS1 or PS2 as catalytic subunits). This process yields various lengths of Aβ fragments, with Aβ40 and Aβ42 being the predominant. The toxicity mechanism of Aβ aggregates remains uncertain, but different perspectives exist.

Tau protein hypothesis

As a major component of NFTs, tau protein exhibits a spatial and temporal distribution that strongly correlates with clinical symptoms, making it a highly specific pathological biomarker in AD patients. Under pathological conditions, an imbalanced activity of phosphatases and kinases leads to hyperphosphorylation of tau leading to the detachment of tau protein from microtubules, followed by conformational changes and mislocalization, accumulation of tau oligomers, paired helical filaments (PHFs), and NFTs within the cell body and dendrites. These changes impair neuronal function and cause cell death.

The neuroinflammation hypothesis

Chronic inflammation in the brain contributes significantly to Alzheimer's disease. This inflammation is driven by activated microglia, the brain's immune cells, which release harmful cytokines when triggered by amyloid plaques. This process creates a vicious cycle, further promoting inflammation and neuronal damage.. Furthermore, neuroinflammation contributes to the development of tau pathology

The oxidative stress hypothesis

An imbalance between reactive oxygen species (ROS) production and the antioxidant defense system contributes significantly to the pathogenesis of AD. In AD patients, factors such as metal accumulation, overexpression of related enzymes, and mitochondrial dysfunction lead to excessive ROS production, resulting in oxidative damage to neuronal membranes, proteins, and nucleic acids. This oxidative stress is believed to initiate a cascade of pathological events, including the promotion of amyloid-β (Aβ) production and tau phosphorylation, activation microglia, triggering a neuroinflammatory cycle that exacerbates neuronal damage,

The cholinergic hypothesis

Damage to cholinergic neurons in the nucleus basalis of Meynert leads to a significant decrease in acetylcholine levels, which is closely associated with cognitive impairments observed in AD. This hypothesis highlights the relationship between cholinergic deficits and the presence of senile plaques, suggesting that the loss of cholinergic function contributes to the cognitive decline seen in AD patients.

The metal ion hypothesis

Dysregulation of trace metals, particularly iron, copper, and zinc, is closely associated with AD pathology. Inappropriate accumulation of these metals can disrupt neuronal metal ion homeostasis, leading to oxidative stress and neuronal damage. The presence of these metals in amyloid plaques and neurofibrillary tangles can modulate enzyme activity and disrupt protein clearance pathways, further exacerbating AD pathology.

The microbiota-gut-brain axis hypothesis

The gut microbiome may influences brain function and behavior through various pathways, including metabolic, endocrine, neural, and immune interactions . Dysbiosis, or an imbalance in the gut microbiota, can compromise the intestinal barrier, allowing harmful substances to enter the bloodstream and trigger systemic inflammation that may cross the blood-brain barrier, affecting microglial function and exacerbating neuroinflammation in the brain.

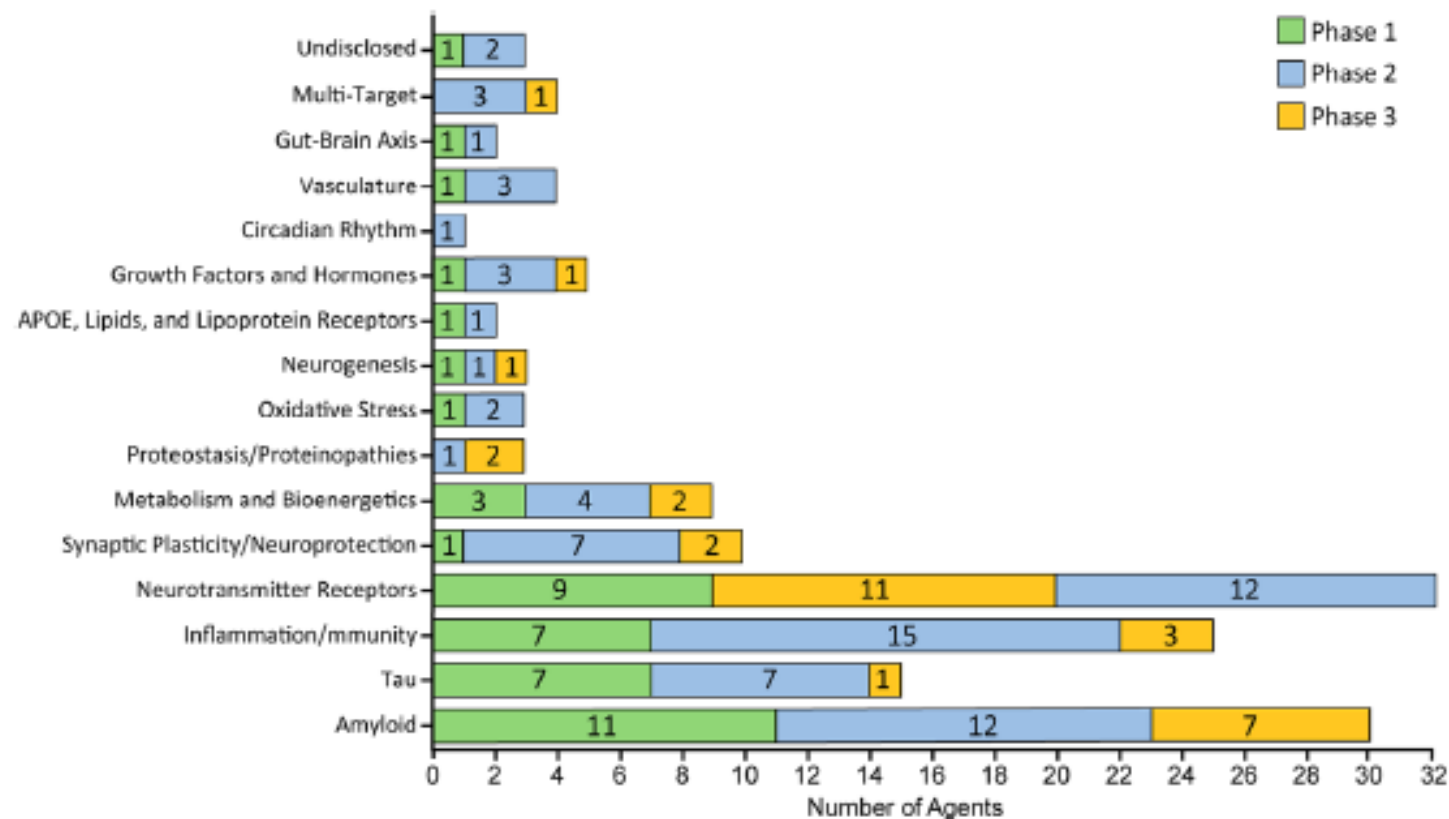
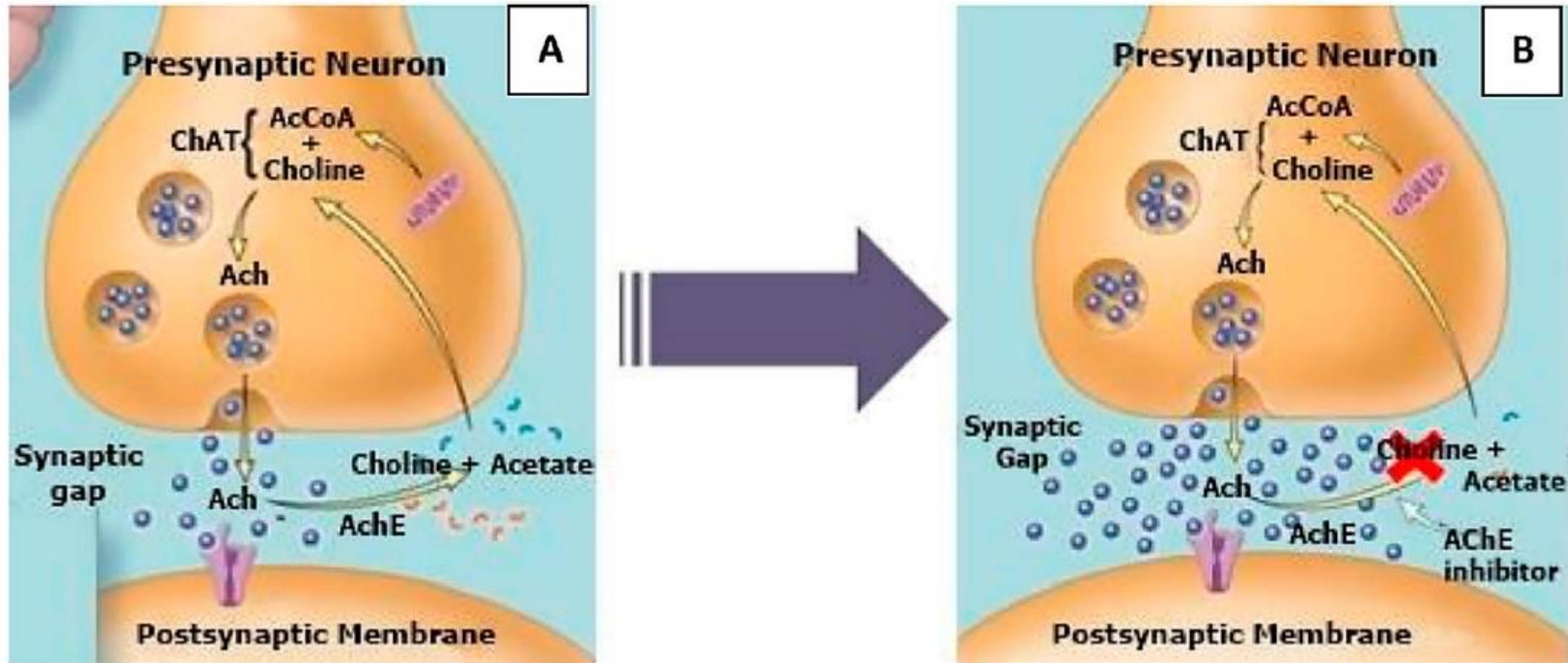


FIGURE 2 Alzheimer-related processes as categorized by the Common Alzheimer's Disease Research Ontology (CADRO) for agents in each phase of the Alzheimer's drug development pipeline (J. Cummings; M. de la Flor, PhD, Illustrator).

Treatment (management) of dementia (in elderly)

- Life style modifications (*physical activity, nutrition, social network, etc*)
- Patients' and caregivers' education and support
- Assessment and management of frailty
- Treatment of somatic diseases (*avoiding overmedication*)
- **Specific pharmacological treatment**
- NPS treatments (pharmacological and not pharmacological)
- Rehabilitation and physical, cognitive and behavioural stimulations
- Caregivers
- Socio-economic interventions, institutionalization
- Ethical decisions



General scheme of the cholinergic hypothesis for AChE inhibition. (A) Low concentrations of acetylcholine in the synaptic gap. (B) Increase in concentration after inhibition of AChE.

**2025
ALZHEIMER'S DISEASE
FACTS AND FIGURES**

U.S. Food and Drug Administration-Approved Treatments for Alzheimer's Disease

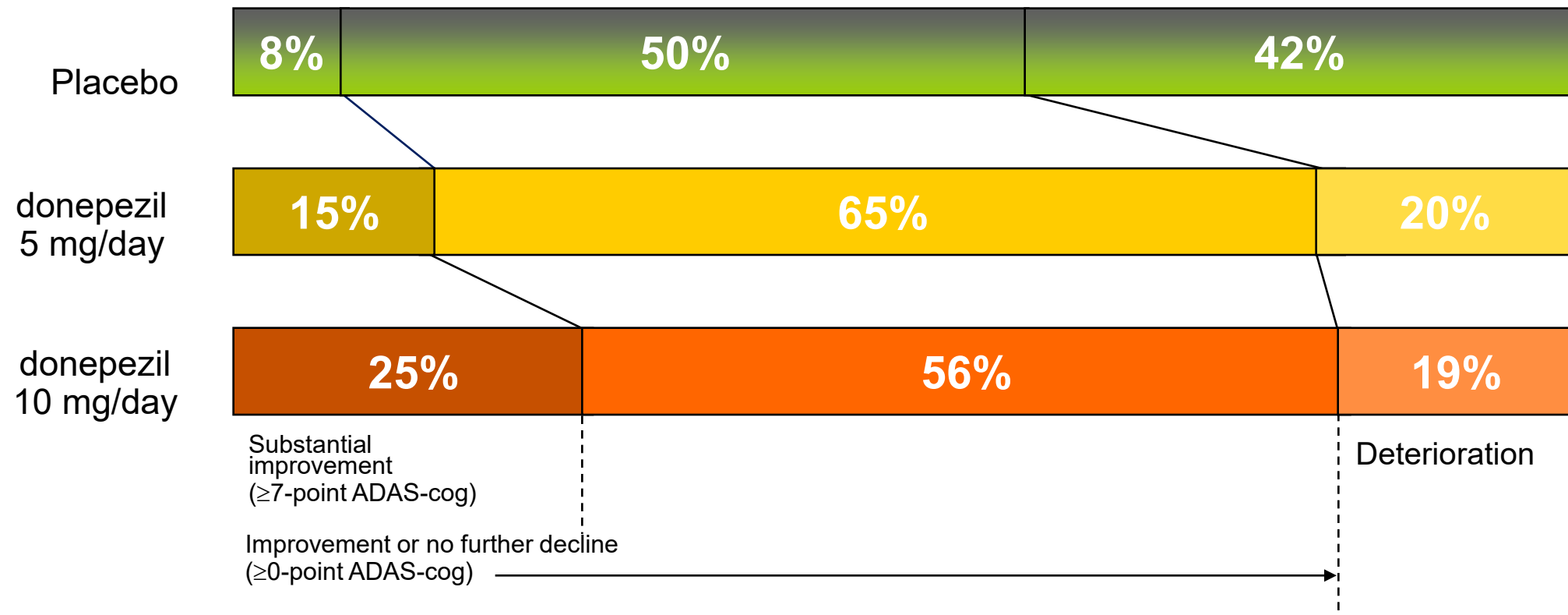
Treatment					
	Asymptomatic or Subtle Cognitive Change (Stages 0-2)	Mild Cognitive Impairment (Stage 3)	Mild Dementia (Stage 4)	Moderate Dementia (Stage 5)	Severe Dementia (Stage 6)
1996 Donepezil (Aricept®)			Treat symptoms (cognition and function)		
2000 Rivastigmine (Exelon®)			Treat symptoms (cognition and function)		
2001 Galantamine (Razadyne®)			Treat symptoms (cognition and function)		
2003 Memantine (Namenda®)				Treat symptoms (cognition and function)	
2014 Memantine + Donepezil (Namzaric®)				Treat symptoms (cognition and function)	
2020 Suvorexant* (Belsomra®)			Treat symptoms (behavior)		
2023 Lecanemab (Leqembi®)		Slow disease progression (cognition, function and behavior)			
2023 Brexpiprazole (Rexulti®)			Treat symptoms (mood)		
2024 Donanemab (Kisunla™)		Slow disease progression (cognition, function and behavior)			

*Approved for insomnia, not Alzheimer's, but safe and effective in people living with Alzheimer's.

Donepezil US, 30-week, Phase III trial

ADAS-cog Results: A Responder Analysis

Comparison of response patterns with donepezil treatment*



*Based upon the best score attained by each patient during the study

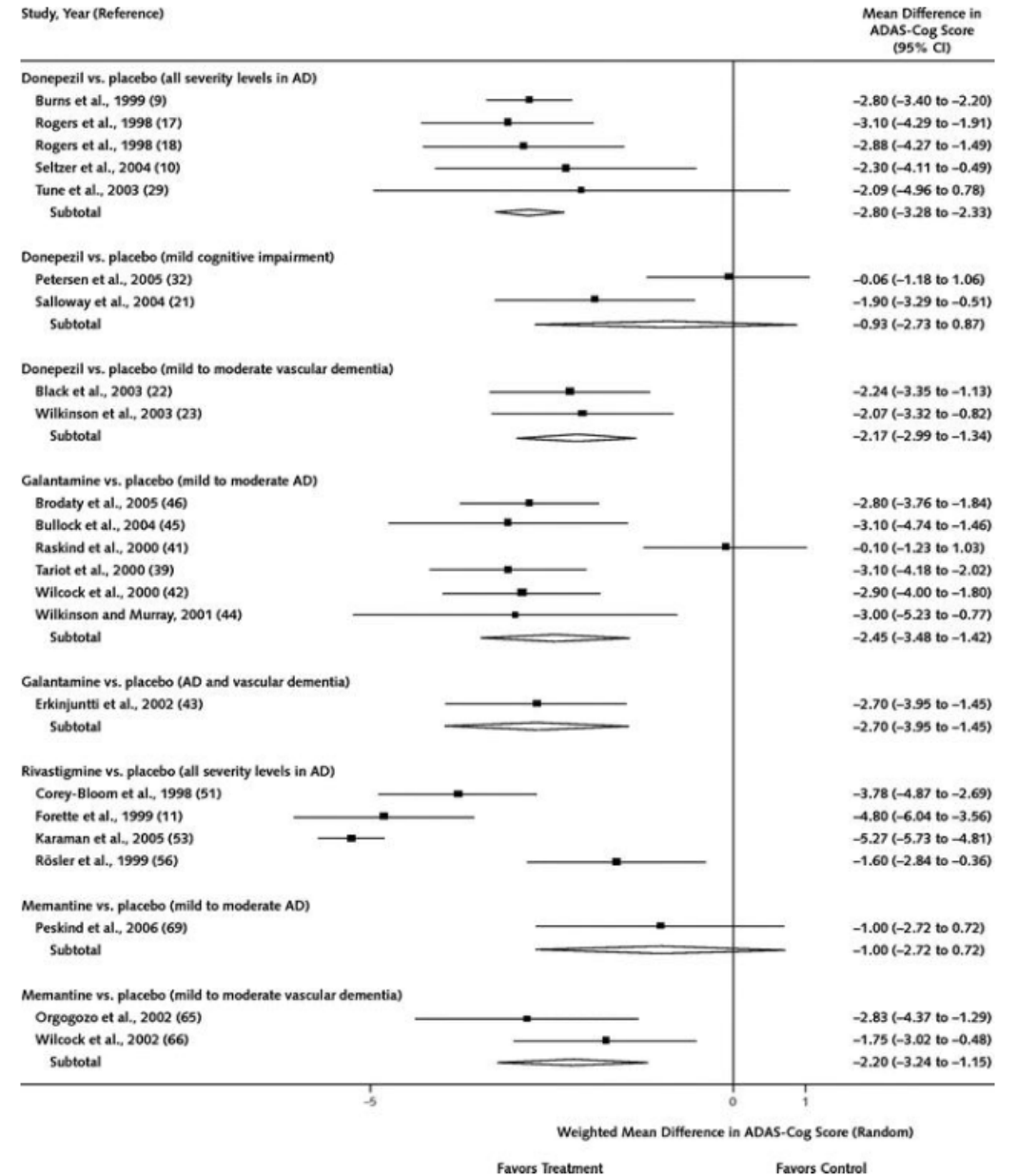
Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline FREE

Authors: Parminder Raina, PhD, Pasqualina Santaguida, PhD, Afisi Ismaila, MSc, Christopher Patterson, MD, David Cowan, MD, Mitchell Levine, MD, Lynda Booker, BSc, and Mark Oremus, PhD | [AUTHOR, ARTICLE, & DISCLOSURE INFORMATION](#)

96 publications representing 59 unique studies were eligible for this review. Both cholinesterase inhibitors and memantine had consistent effects in the domains of cognition and global assessment, but summary estimates showed small effect sizes. Outcomes in the domains of behavior and quality of life were evaluated less frequently and showed less consistent effects. Most studies were of short duration (6 months), which limited their ability to detect delay in onset or progression of dementia. Three studies directly compared different cholinesterase inhibitors and found no differences in cognition and behavior.

Conclusions:

Treatment of dementia with cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia.



Summary estimates for the change in Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) scores.



OPEN Acetyl-cholinesterase-inhibitors slow cognitive decline and decrease overall mortality in older patients with dementia

Marco Zuin¹, Antonio Cherubini², Stefano Volpato³, Luigi Ferrucci⁴ & Giovanni Zuliani^{1,2,3}

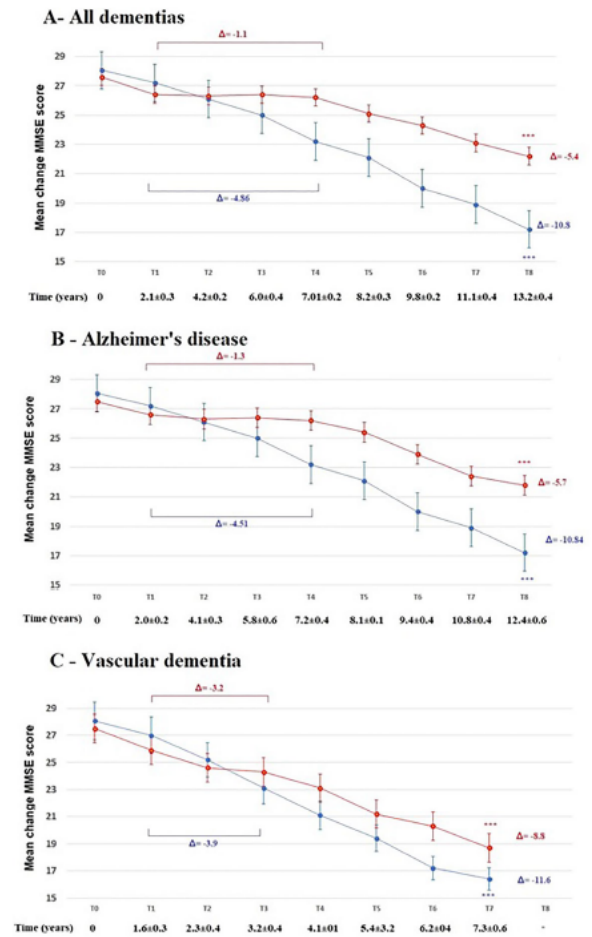


Figure 2. Mini Mental State Examination (MMSE) score during follow-up in all patients with dementia (A), LOAD (B), and vascular dementia (C) according to treatment with AChEIs. *** $p < 0.001$ for trend (Adjusted curves—for propensity score matched cohorts).

Among older people with dementia, treatment with AChEIs was associated with a slower cognitive decline and with reduced mortality, after a mean follow-up of almost eight years. Our data support the effectiveness of AChEIs in older patients affected by these types of dementia.

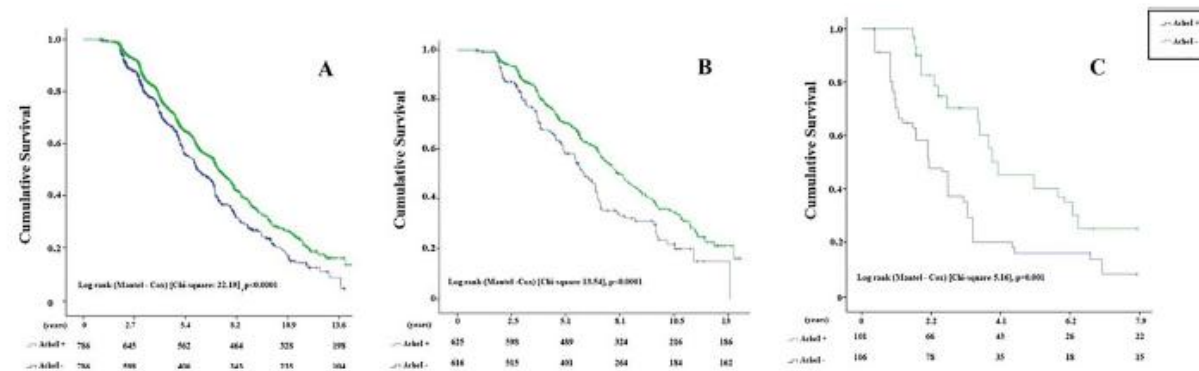


Figure 3. Cumulative survival (Cox multivariate regression analysis) after propensity score matching in patients with dementia treated or not treated with AChEIs (A) all patients; (B) LOAD; (C) vascular dementia.




Treatment for Alzheimer's disease

Nick C Fox, Christopher Belder, Clive Ballard, Helen C Kales, Catherine Mummery, Paulo Caramelli, Olga Ciccarelli, Kristian S Frederiksen, Teresa Gomez-Isla, Zahinoor Ismail, Claire Paquet, Ronald C Petersen, Robert Perneczky, Louise Robinson, Ozge Sayin, Giovanni B Frisoni



- Long-term efficacy data of cholinesterase inhibitors in non-randomised studies show **MMSE decline of 0 · 2–1 · 4 points per year in patients who were treated versus 1 · 1–3 · 4 points in patients who were not treated, with a reduction in relative risk of mortality of 27–42% over 2–8 years.**
- Continued donepezil use is linked to **cognitive and functional benefits**, and less nursing home placement.
- Treatment with **memantine**, has also shown a **small beneficial effect on cognition** in patients with AD who have moderate to severe cognitive impairment. **The incidence of agitation was significantly lower** in memantine versus placebo.
- **Memantine is frequently used in combination with donepezil**, and observational and network meta-analytical data have found better outcomes over monotherapy
- Cholinesterase inhibitors and memantine have shown modest direct patient-reported effects on QoL. **Indirect effects on QoL** might be evident through delayed decline in cognition, behaviour, and function, and reduced hospitalisation or nursing home placement.
- The use of cholinesterase inhibitors and memantine has shown **to improve caregiver burden and caregiver QoL.**
- **Absence or loss of treatment response is the most common guideline-recommended reason for discontinuation**, but rigorous discontinuation trials are needed.

Acetyl-cholinesterase-inhibitors reconsidered. A narrative review of post-marketing studies on Alzheimer's disease

Giovanni Zuliani¹ · Marco Zuin¹ · Tommaso Romagnoli¹ · Michele Polastri¹ · Carlo Cervellati¹  · Gloria Brombo¹

Aging Clinical and Experimental Research (2024) 36:23

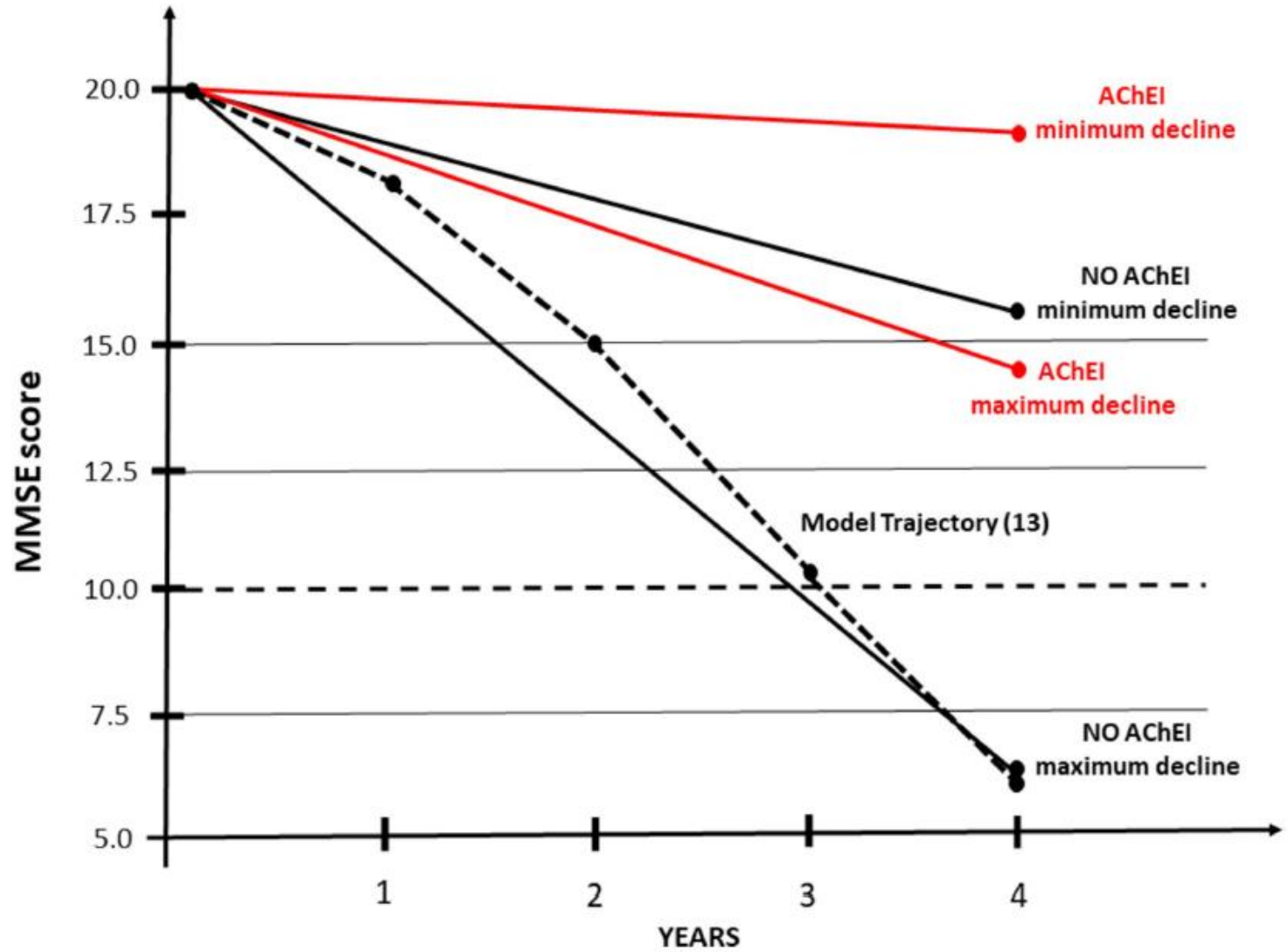


Fig. 1 minimum and maximum mean loss in MMSE score in patients with AD treated or not-treated with AChEI, in a period of 4 years, as derived from the studies reported in the present study. The mean

MMSE loss as calculated by the model of Mendiondo et al. [9] is also reported (dashed line)

Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia (Review)

Parsons C, Lim WY, Loy C, McGuinness B, Passmore P, Ward SA, Hughes C

Parsons C, Lim WY, Loy C, McGuinness B, Passmore P, Ward SA, Hughes C.
Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia.
Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD009081.
DOI: [10.1002/14651858.CD009081.pub2](https://doi.org/10.1002/14651858.CD009081.pub2).

This review suggests that discontinuing cholinesterase inhibitors may result in worse cognitive, neuropsychiatric and functional status than continuing treatment, although this is supported by limited evidence, almost all of low or very low certainty. As all participants had dementia due to Alzheimer's disease, our findings are not transferable to other dementia types. We were unable to determine whether the effects of discontinuing cholinesterase inhibitors differed with baseline dementia severity.

Although there was uncertainty about the results, most of the evidence pointed to benefits of continuing treatment with cholinesterase inhibitors.

We found no trials that just investigated stopping memantine.

These results may help patients and their doctors to make decisions about whether or not to continue treatment, although other factors, such as side effects in an individual patient and the patient's preferences, are also important.

Side effects of ache-i and memantine in AD

Side Effect	Donepezil	Galantamine	Rivastigmine (Oral)	Rivastigmine (Patch)	Memantine
Nausea	3 – 19%	13 – 24%	29 – 47%	7 – 21%	2%
Diarrhea	5 – 15%	6 – 12%	15 – 19%	6 – 10%	5%
Dizziness	8%	9%	19 – 21%	2 – 7%	5 – 7%
Insomnia	5 – 14%	5%	9%	Low	2%
Bradycardia	1 – 3%	1%	1%	<1%	Very Rare
AV block	0.1-1%	0.1%	0.1-1%	0.1%	0.1%
Syncope (Fainting)	0.8 – 2%	0.5 – 1%	1 – 2%	<1%	<1%

Kröger, E. et al. *Systematic Reviews*, 2025; 14(1), 42–58.

Wang, J., et al 2024; *Advances in Clinical and Experimental Medicine*, 33(2), 145–158.

Yaghmaei, E., et al. 2024; *Frontiers in Pharmacology*, 15, 1342501

Summary of Pharmacological Treatments for Cognitive Symptoms

Overview of Treatments

Pharmacological treatments for cognitive symptoms have been generally well-tolerated, with no significant adverse events reported.

Recommendations for Alzheimer's Disease Treatment

Cholinesterase Inhibitors: It is recommended to offer monotherapy with one of the three cholinesterase inhibitors (donepezil, galantamine, rivastigmine) for mild to moderate Alzheimer's disease, with a strong positive recommendation.

Donepezil for Moderate to Severe Cases: Donepezil is recommended for moderate to severe Alzheimer's disease, albeit with a weak positive recommendation.

Memantine Use: Memantine should be offered to patients with moderate Alzheimer's who cannot tolerate cholinesterase inhibitors or have severe disease, also with a weak positive recommendation.

Specialist Prescription: Treatment initiation should be guided by specialists (neurologists, geriatricians, psychiatrists) within Cognitive Disorders and Dementia Centers, ensuring appropriate expertise.

Treatment (management) of dementia (in elderly)

- Life style modifications (*physical activity, nutrition, social network, etc*)
- Patients' and caregivers' education and support
- Assessment and management of frailty
- Treatment of somatic diseases (*avoiding overmedication*)
- Specific pharmacological treatment
- **NPS treatments (pharmacological and not pharmacological)**
- Rehabilitation and physical, cognitive and behavioural stimulations
- Caregivers
- Socio-economic interventions, institutionalization
- Ethical decisions

Elementi per la decisione terapeutica dei BPSD



2014

- **Evidenza di declino cognitivo**, valutazione sindromica e etiologica, stadiazione cognitive e funzionale
- **Profilo dei BPSD** (frequenza, gravità, clusterizzazione, persistenza, modalità di emergenza)
- **Rischi** per il paziente e per i caregiver
- **Sofferenza** del paziente (insight) e del caregiver (?)
- **Comorbidità e trattamenti** in atto (con attenzione alla storia psichiatrica e all'abuso di sostanze)
- **Eventi scatenanti-stressors** (comportamenti di altri, malattie fisiche o sintomi (es dolore, stipsi), farmaci, trattamenti non farmacologici, ambiente)
- **Caregiving** (formale e informale)
- **Setting** (casa, NH, ospedale, CDI....)

The Lancet Series on Alzheimer's Disease 2



Treatment for Alzheimer's disease

Nick C Fox, Christopher Belder, Clive Ballard, Helen C Kales, Catherine Mummery, Paulo Caramelli, Olga Ciccarelli, Kristian S Frederiksen, Teresa Gomez-Isla, Zahinoor Ismail, Claire Paquet, Ronald C Petersen, Robert Perneczky, Louise Robinson, Ozge Sayin, Giovanni B Frisoni



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Stressor-associated BPSD and BPSD likely due to neurodegeneration

The successful treatment of BPSD relies on correctly identifying the relevant stressors

Non-pharmacological treatments for BPSD

Personalised activities and enjoyable exercise have shown benefits for depression and apathy... In stressor-associated BPSD, improved communication, good use of nonverbal skills, and planning to avoid specific trigger situations are usually the most effective approaches. Psychological interventions have been less effective in directly improving psychotic symptoms.

Pharmacological treatments

In medicine, few areas show as large a gap between evidence and practice as pharmacological treatment of BPSD.

Antipsychotics for nursing home residents with dementia: Chemical restraints or essential therapeutic intervention?

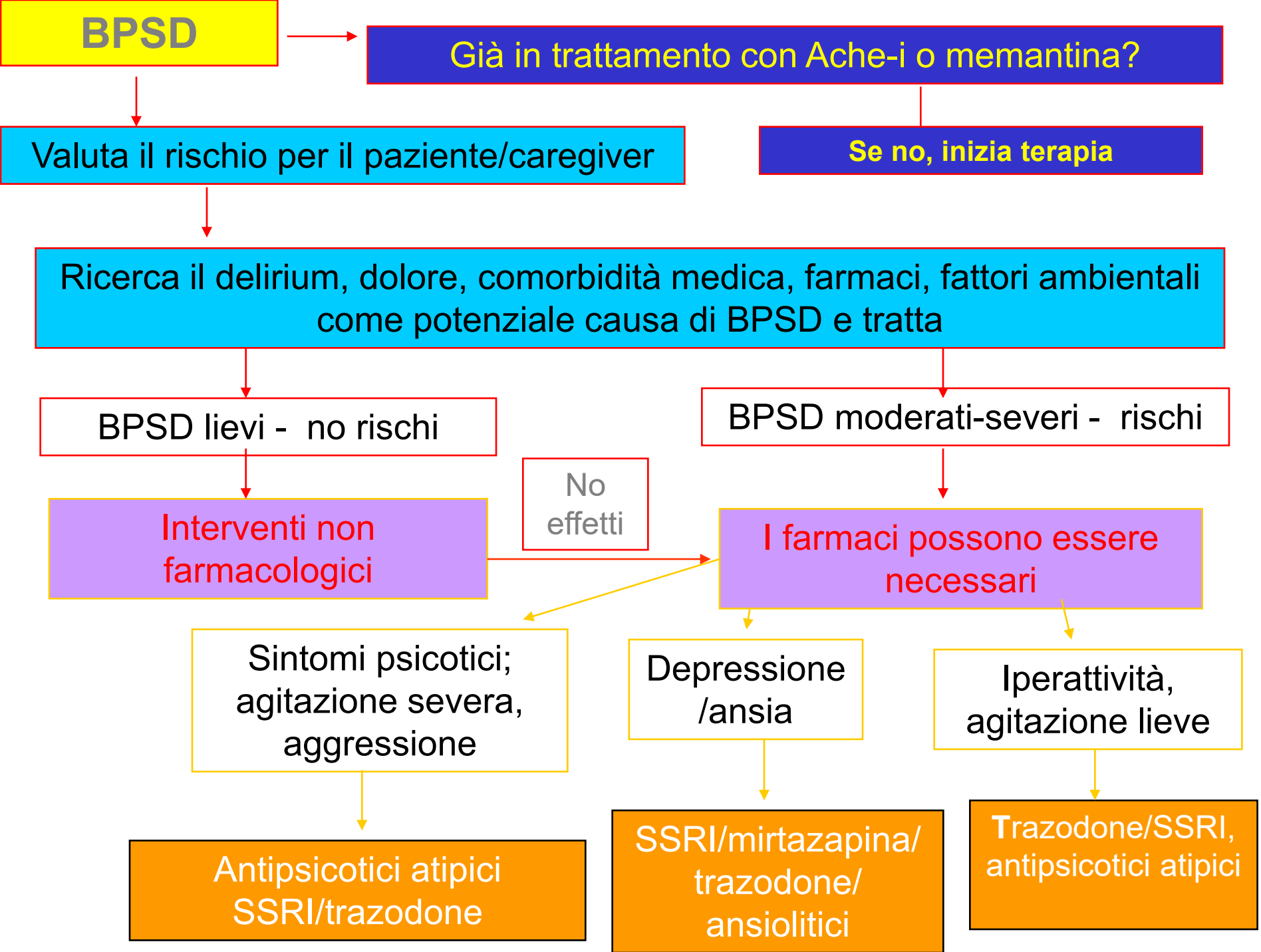
The use of antipsychotics as “chemical restraints” in nursing home residents with BPSD has been discussed in the medical literature and lay press for decades. Many studies document that these drugs are associated with an increase in all-cause mortality and the risk of stroke and myocardial infarction... Non-pharmacologic interventions ... have been shown to be effective in some studies, but they can be challenging to implement, due to limited staff and frequent staff turnover. Another strategy ... (antiepileptic drugs, pain treatment...)... are ineffective...

To be sure, there is substantial amount of inappropriate prescription of antipsychotic drugs in U.S. nursing homes, and they are still some cases in which these drugs are used as “chemical restraints”. But there is a flip side to the story. **For some nursing home residents, not just those who have a well-documented exclusionary diagnosis, antipsychotics can be an essential therapeutic intervention.**

Residents with moderate and advanced dementia who are “agitated” and “aggressive” are among the most challenging to manage. They often do not have durable responses to re-direction and other non-pharmacologic measures such as physical and social activities, music, and pet therapy.

Here is the rub: **some of these individuals are in fact psychotic, and the use of antipsychotics IS appropriate to prevent danger to themselves or others, to make essential care feasible to perform, to treat intense psychological distress, and to prevent major declines in function and quality of life.**

So, **are antipsychotics in nursing home residents with dementia chemical restraints or an essential therapeutic intervention?** My answer is the two words ... **“It depends”**. ... Geriatrics is all about person-centered care. If the patient/resident has a well documented qualifying diagnosis, or has another appropriate indication for prescribing an antipsychotic, and they or their surrogate decision-maker perceives that the benefits of drug treatment outweigh the risks given their preferences, willing to take risks, and their previous experiences, **then prescription of an antipsychotic should be considered an essential therapeutic intervention when non-pharmacologic interventions are ineffective, not a chemical restraint.**



2014



Table 2. Treatments Commonly Used for Neuropsychiatric Syndromes in Neurodegenerative Disorders^a

Behavior	Therapeutic class	Agents ^b	Type of supportive evidence
Psychosis	Antipsychotics	Pimavanserin (psychosis of PD) ^c	Double-blind, placebo-controlled trials
		Aripiprazole	Double-blind, placebo-controlled trials
		Risperidone	Double-blind, placebo-controlled trials
Agitation	Antipsychotics	Brexpiprazole (agitation with dementia due to AD) ^c	Double-blind, placebo-controlled trials
		Aripiprazole	Double-blind, placebo-controlled trials
		Risperidone	Double-blind, placebo-controlled trials
		Quetiapine	Mixed outcomes of double-blind, placebo-controlled trials
	Antidepressants	Citalopram	Double-blind, placebo-controlled trials
	Anticonvulsants	Carbamazepine	Double-blind, placebo-controlled trials
Apathy	Stimulants	Methylphenidate	Double-blind, placebo-controlled trials
		Modafanil	Multiple case observations
Depression	Selective serotonin reuptake inhibitors (for PD)	Paroxetine	Double-blind, placebo-controlled trials in PD
	Selective serotonin and norepinephrine reuptake inhibitors (for PD)	Venlafaxine	Double-blind, placebo-controlled trials
	Selective serotonin reuptake inhibitors and serotonin receptor modulators	Vortioxetine	Open-label clinical trial
	Dopamine agonists	Pramipexole (for PD)	Double-blind, placebo-controlled trials
	Seizure induction	ECT	Multiple case observations
Disinhibition	Antidepressants	Citalopram	Open-label clinical trial
	Anticonvulsants	Valproic acid	Case reports
	Miscellaneous	Methylphenidate	Double-blind, placebo-controlled crossover trial
		Dextromethorphan plus quinidine	Case reports

Diagnosi e trattamento di demenza e *Mild Cognitive Impairment*

Data di pubblicazione: ottobre 2023
Data di aggiornamento previsto: dicembre 2026


- Assoluta necessità di valutare attentamente ed in modo specifico le possibili cause di disagio della persona con demenza allo scopo di individuare possibili cause ambientali o fisiche, in particolare dolore, delirium, trattamenti inappropriati e assistenza inadeguata, che sostengano una condizione di disagio, agitazione, aggressività, disturbi del sonno e più in generale disturbi psichici e comportamentali che si associno al quadro di disturbi cognitivi della persona.
- Il GdL sottolinea la necessità di un uso attento e ponderato dei farmaci psicotropi nelle persone con demenza, che deve considerare sempre, oltre alla corretta indicazione alla prescrizione, la valutazione del bilancio tra efficacia e rischio di comparsa di effetti collaterali.
- In relazione all'uso di antipsicotici il GdL sottolinea come complessivamente l'analisi, in studi di affidabilità moderata, mostri prove chiare di efficacia in relazione alla riduzione del sintomo definito globalmente "agitazione" oltre che più in general dei BPSD (valutazione di esito con NPI e CMAI), associate tuttavia a evidente aumento in frequenza di eventi avversi di tutti i tipi e, in alcuni casi, di mortalità. In particolare, va sottolineato come la maggior parte degli studi inclusi sia rivolto al trattamento dell'agitazione piuttosto che al trattamento dei quadri di psicosi.

Diagnosi e trattamento di demenza e *Mild Cognitive Impairment*

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- Il trattamento con aloperidolo non ha prodotto miglioramento né dei livelli di agitazione né dei disturbi comportamentali.
- Pimavanserina e brexpiprazolo hanno dimostrato una efficacia su sintomi psicotici e livelli di agitazione, a fronte di un aumento del rischio di eventi avversi. Ù
- Riguardo aripiprazolo, il trattamento a diverse dosi del farmaco migliora BPSD, sintomi psichiatrici, livelli di agitazione, ma è evidente un aumento della sonnolenza.
- Quetiapina, somministrata a diverse dosi, fino a un massimo di 200 mg/die, migliora i BPSD (esiti con NPI), in studi di affidabilità moderata con un aumento di eventi avversi caratterizzato principalmente da sonnolenza.
- Risperidone al contrario, ad un massimo di 1,5 mg/die, migliora i livelli di agitazione ma non è efficace su altri BPSD, a fronte di un aumento di eventi avversi extrapiramidali, cerebrovascolari, sonnolenza, ma non mortalità.

Diagnosi e trattamento di demenza e *Mild Cognitive Impairment*



Data di pubblicazione: ottobre 2023
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- L'evidenza di rischi significativi del trattamento con antipsicotici in una popolazione fragile come quella costituita da persone con demenza impone di limitarne l'utilizzo solo alle condizioni rappresentate da un'urgente necessità di trattamento per prevenire danni alla persona con demenza o ad altri e nel caso di gravi quadri di agitazione, allucinazioni o deliri che pongono la persona in una condizione di severo *distress*. In questo senso l'uso sarebbe quindi mirato al trattamento di base della psicosi e sarebbe da ritenersi comunque appropriato al pari di una persona che non abbia una coesistente condizione di demenza.

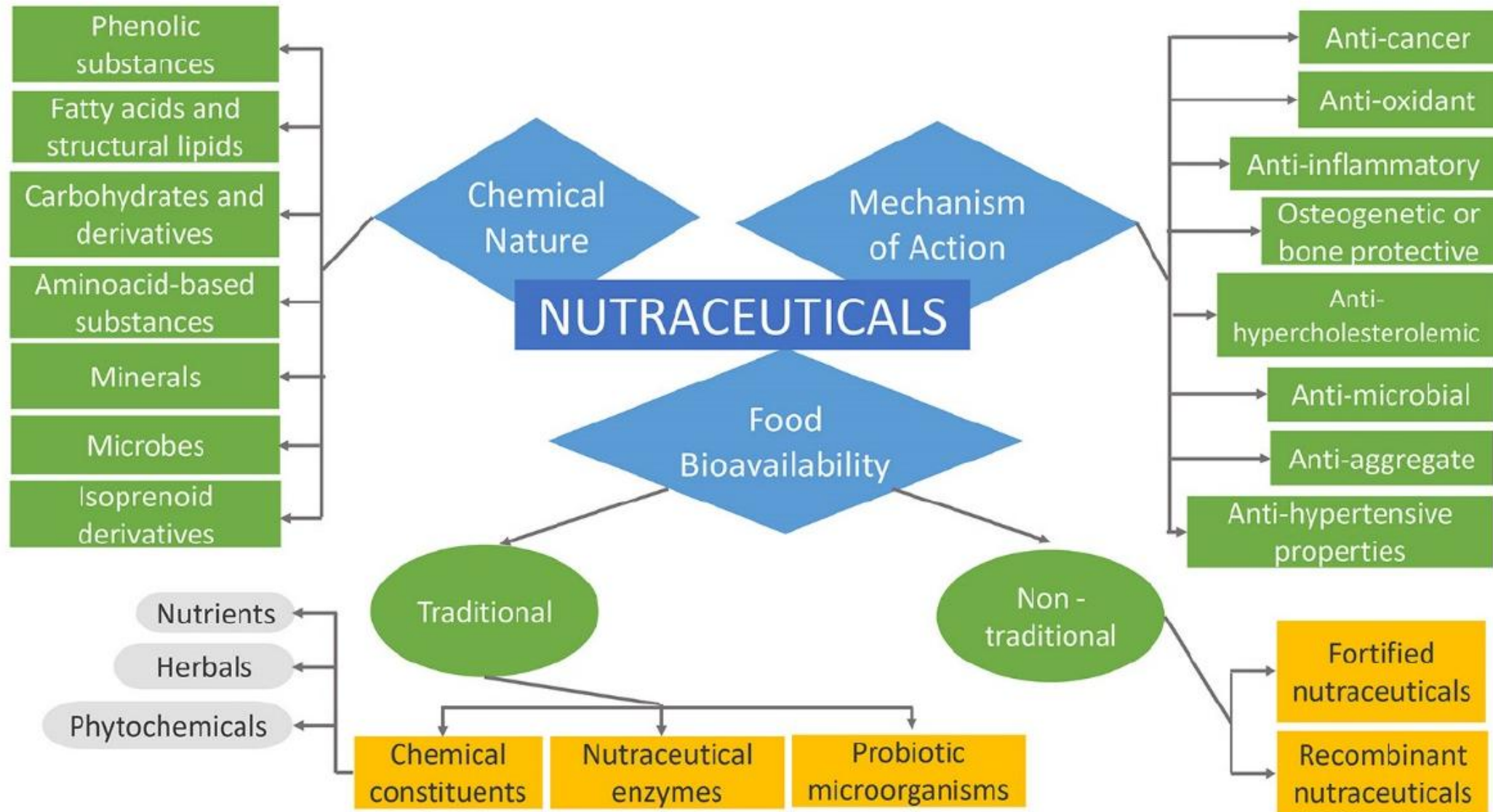
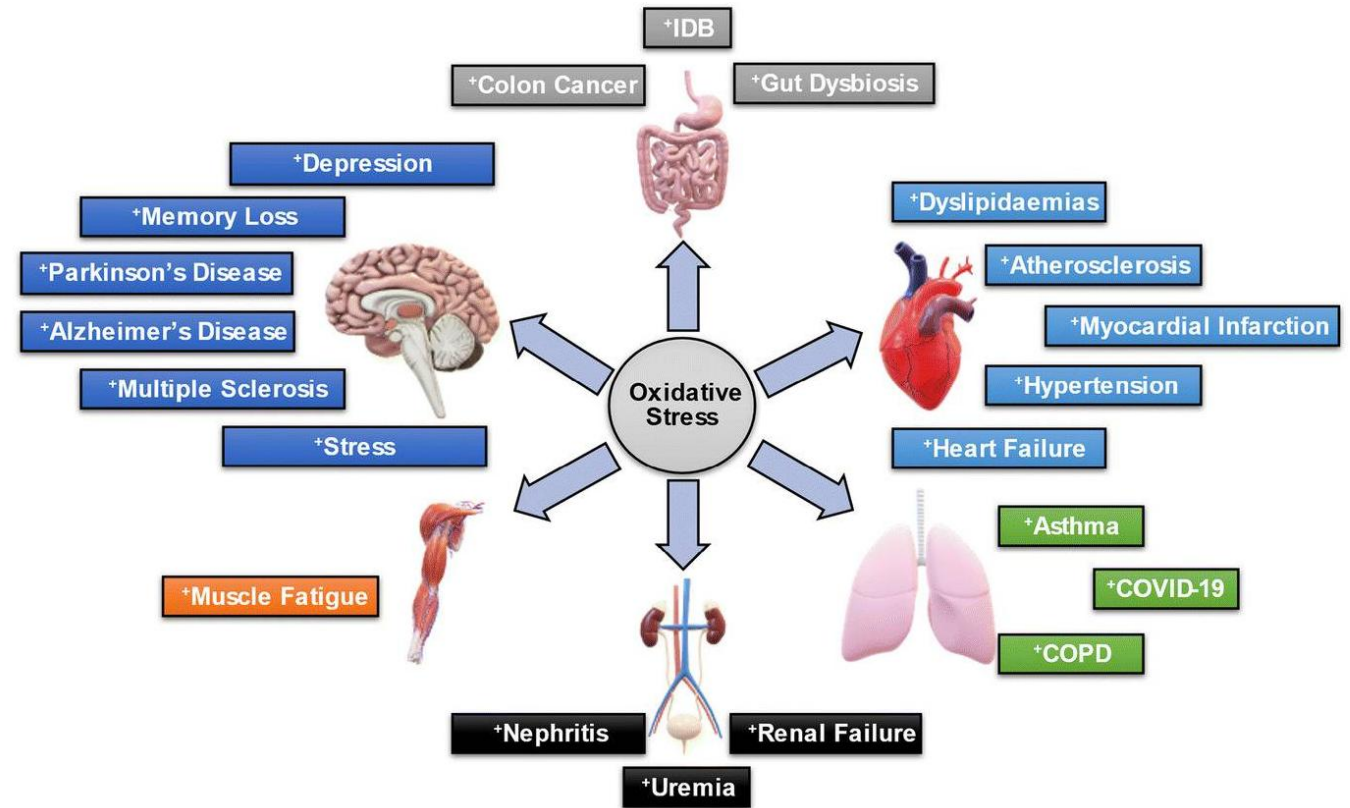


Figure 4. Classification of Nutraceuticals.

Nutraceuticals for aging brain, frailty, inflammaging

- **Polyphenols**
 - Flavonoids, Ginkgo biloba
 - Blueberry and soy flavonoids
 - Resveratrol
 - Curcumin
- **Vitamins and oligoelements**
 - Vitamin C, vitamin E, vitamin D
 - Folic ac and vitamin B
 - Zinc
- **Ω-3 fatty acids**
- **Antioxidants** (Lipoic ac, Glutathione supplements, PEA)
- **Acetyl-L-carnitine**
- **Homotaurine**
- **CDP-choline, Choline alfoscerate, Phosphatidylserine, Fortasyn Connect**

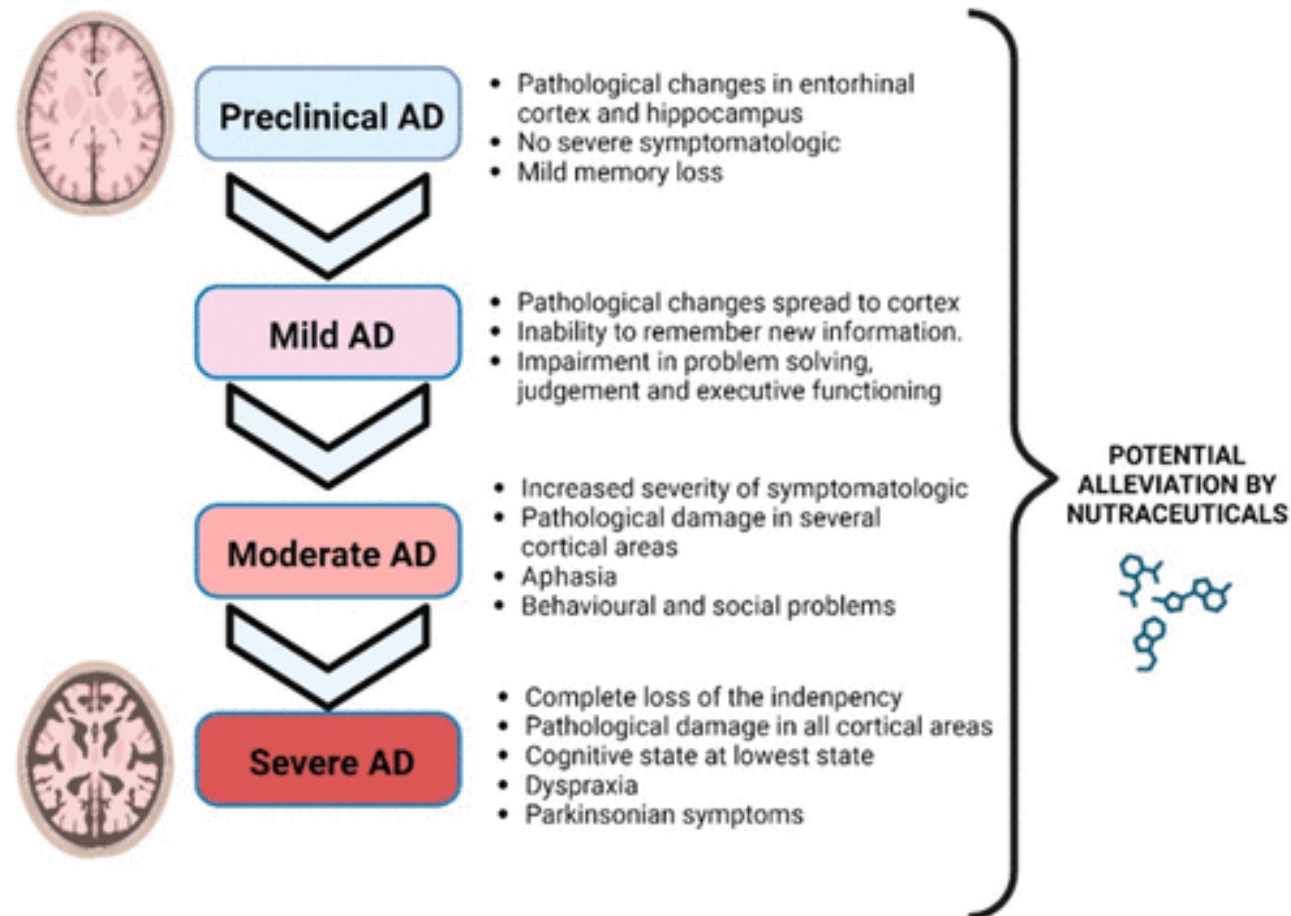


The main mechanisms of action of nutraceuticals against cognitive decline include their ability to influence cellular processes such as **neurogenesis**, **synaptogenesis**, **synaptic transmission**, **neuroinflammation**, **oxidative stress**, **cell death modulation**, and **neuronal survival**.

These compounds have been shown to impact signaling pathways and mechanisms underlying neuroprotective processes, potentially reversing cognitive impairment and mitigating the progression and symptomatology of Alzheimer's disease.

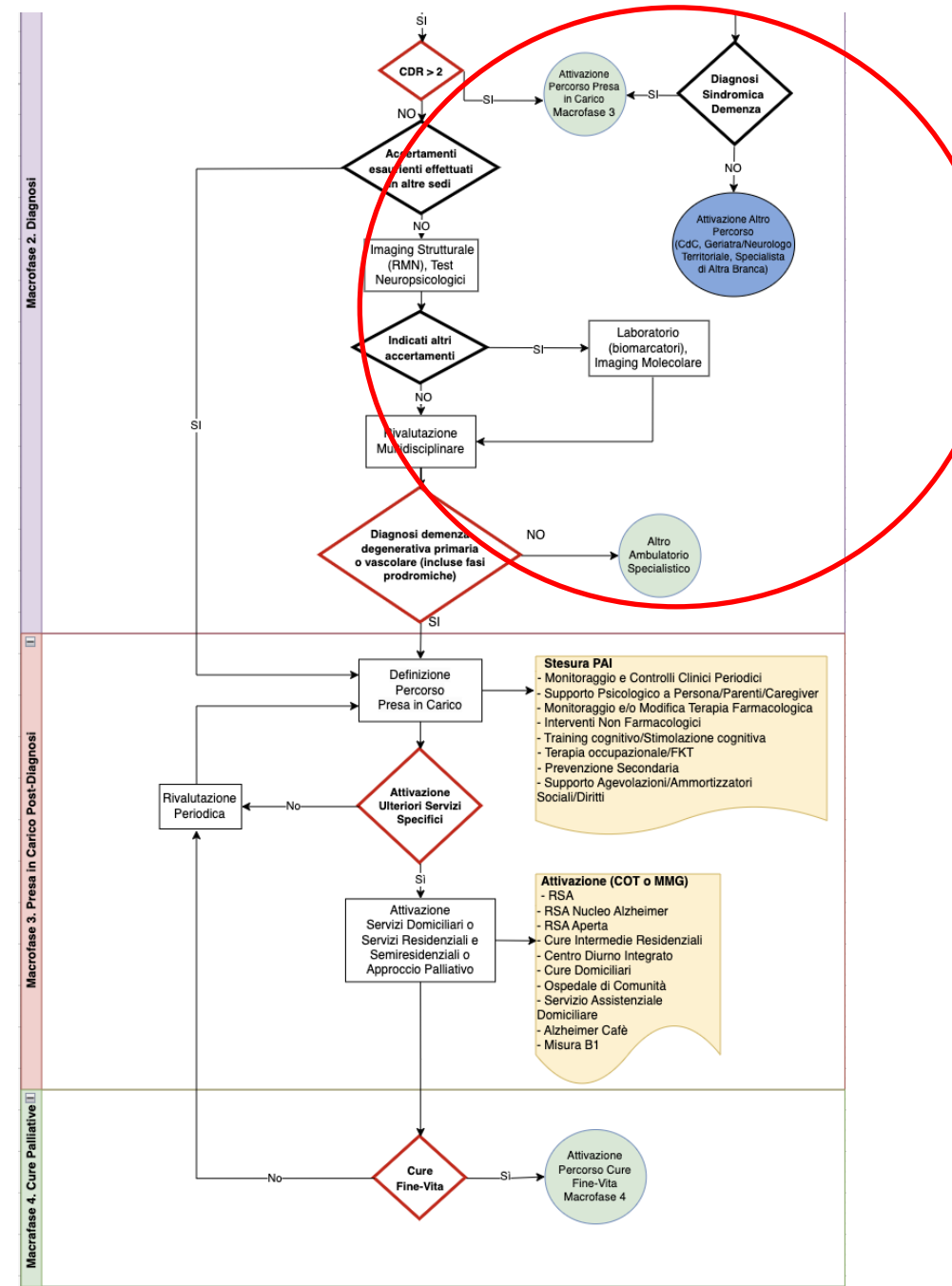
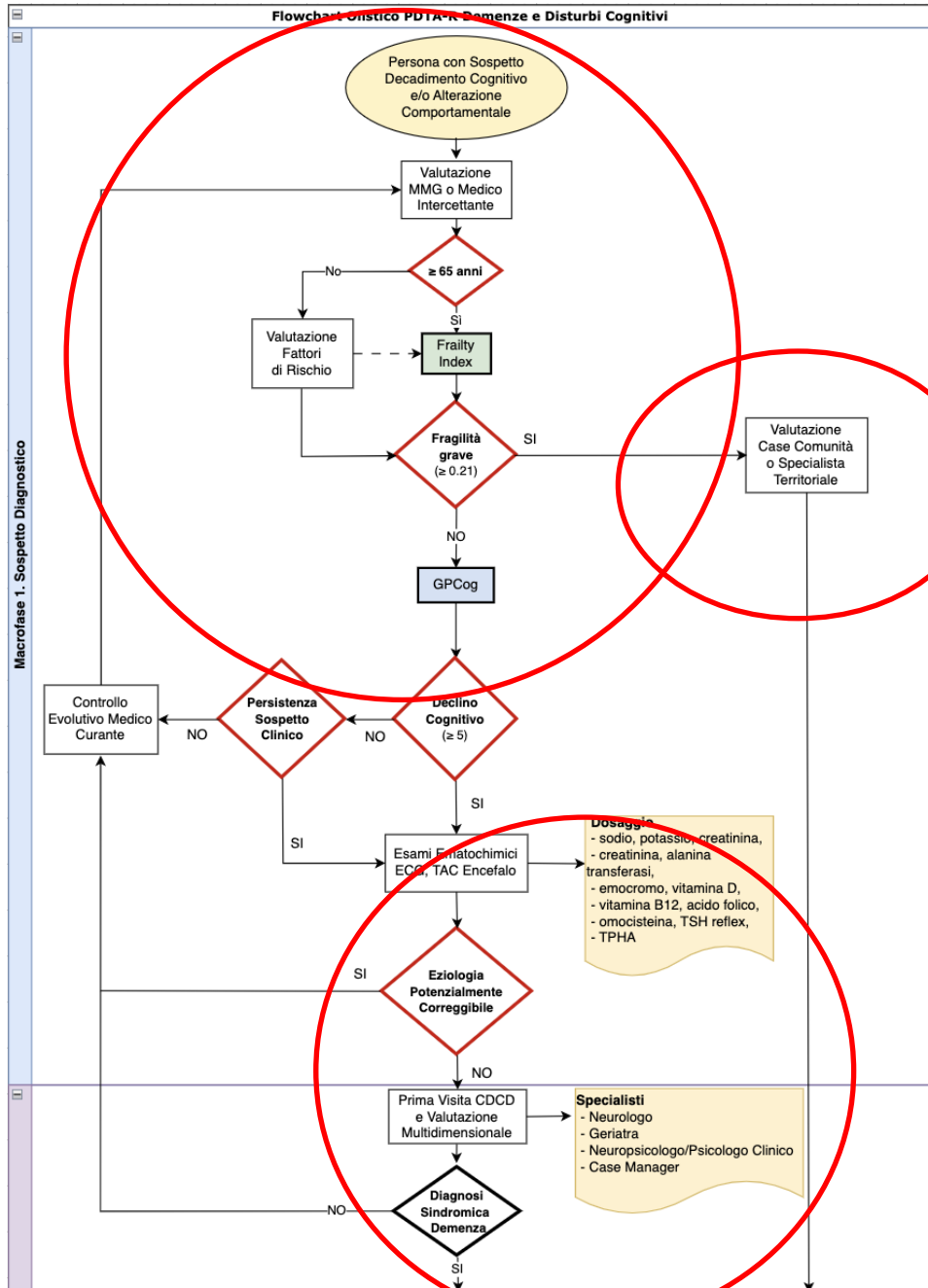
Additionally, nutraceuticals have been found to modulate complex brain functions such as **neuroregeneration**, **neuroprotection**, **neuroplasticity**, **memory**, and **cognition**, making them promising agents for food-based strategies for Alzheimer's disease prevention and cognitive decline management.

NUTRACEUTICALS AGAINST ALZHEIMER'S DISEASE (AD)

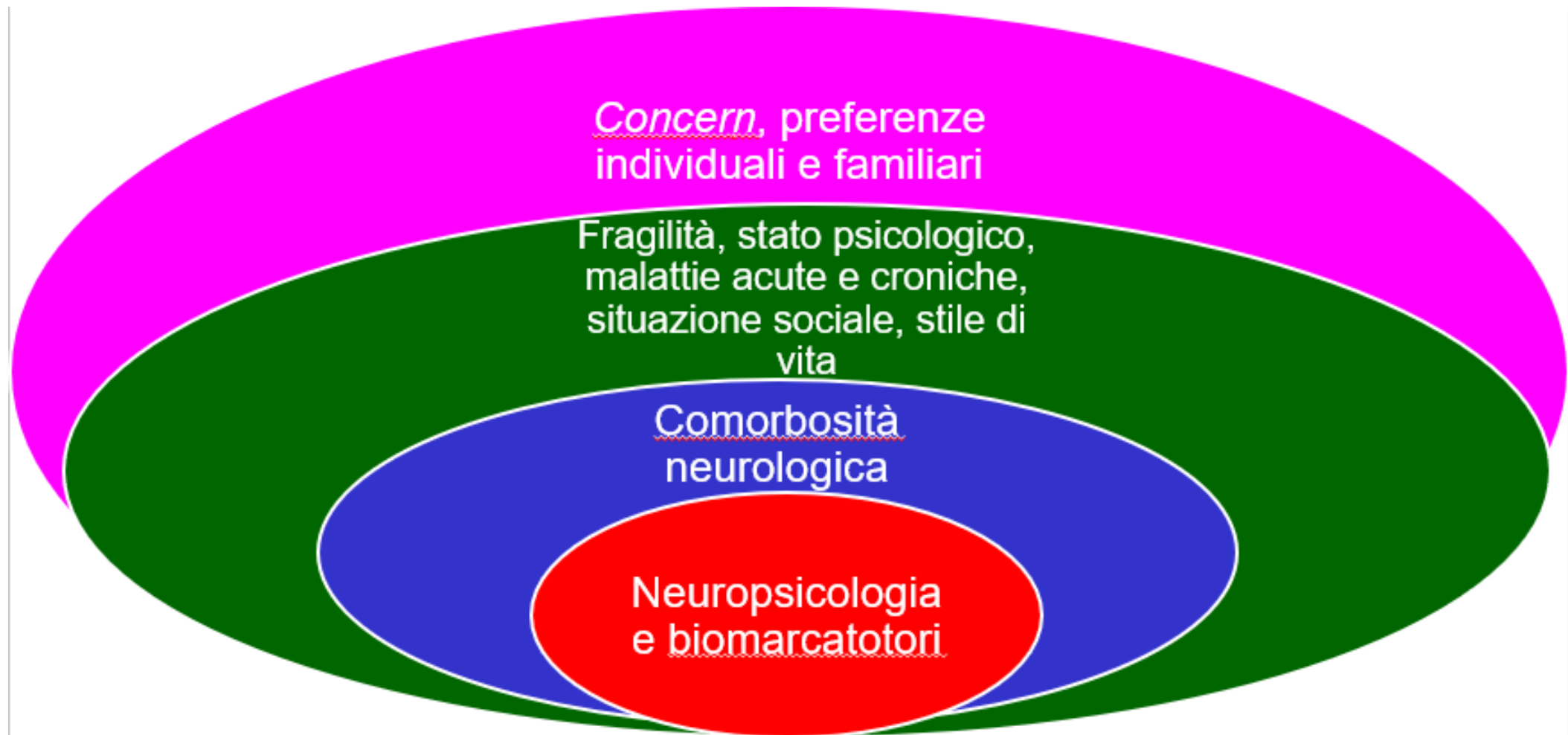


Nutraceutical	Proposed Mechanism of Action	Clinical Evidence Level
Omega-3 (DHA/EPA)	Reduces neuroinflammation; supports cell membrane fluidity.	Moderate/High: Best for prevention and early stages (MCI).
Curcumin	Inhibits amyloid aggregation; potent antioxidant.	Moderate: Limited by poor absorption (bioavailability).
Ginkgo Biloba	Improves microcirculation; acts as a free-radical scavenger.	Moderate: Mixed results; some benefit in mild dementia.
B-Vitamins (B6, B12, Folate)	Reduces Homocysteine (a neurotoxin).	Strong: Crucial for those with high homocysteine levels.
Resveratrol	Activates SIRT1 (longevity genes); protects mitochondria.	Emerging: Strong lab data; clinical results are still mixed.
PEA (Palmitoylethanolamide)	Reduces "neuro-inflammation" via glia cell modulation.	Emerging: Showing promise for behavioral symptoms/pain.
Polyphenols (e.g., EGCG)	Prevents protein misfolding; reduces oxidative stress.	Moderate: Effective as part of a "Mediterranean" diet.
Glutathione	The brain's master antioxidant; detoxifies heavy metals.	Low/Moderate: Oral forms are poorly absorbed (liposomal preferred).
Choline / Citicoline	Precursor to Acetylcholine; repairs neuron membranes.	High (Adjunctive): Often paired with ChEIs for synergy.
Phosphatidylserine	Major structural component of neuron membranes.	Moderate: May improve memory and mood in early AD.
Huperzine A	Natural acetylcholinesterase inhibitor.	Moderate: Works similarly to Donepezil; avoid combining them.
Homotaurine	Competes with A β peptides to prevent plaque formation.	Moderate: Studied specifically for slowing hippocampal atrophy.
Acetyl-L-Carnitine	Boosts mitochondrial energy; supports acetylcholine.	Moderate: May slow decline in younger AD patients.

Workflow Paziente Rete Regionale CDCD



L'approccio all'anziano con decadimento cognitivo



Conclusioni

- L'approccio ai disturbi cognitivo comportamentali nell'anziano richiede un approfondimento diagnostico valutativo come premessa al trattamento
- L'attenzione alla fragilità, alla comorbidità è centrale nell'approccio al paziente anziano con decadimento cognitivo
- Il trattamento con farmaci «tradizionali» (ache-i e memantina) ha ancora uno spazio significativo nella gestione del paziente con malattia di Alzheimer
- La durata del trattamento e le ragioni di sospensione restano ancora un'area di incertezza
- E' necessaria la presa in carico del paziente e della famiglia e della complessità dei loro bisogni
- Chi, come e dove deve essere fatto è ancora oggetto di discussione....