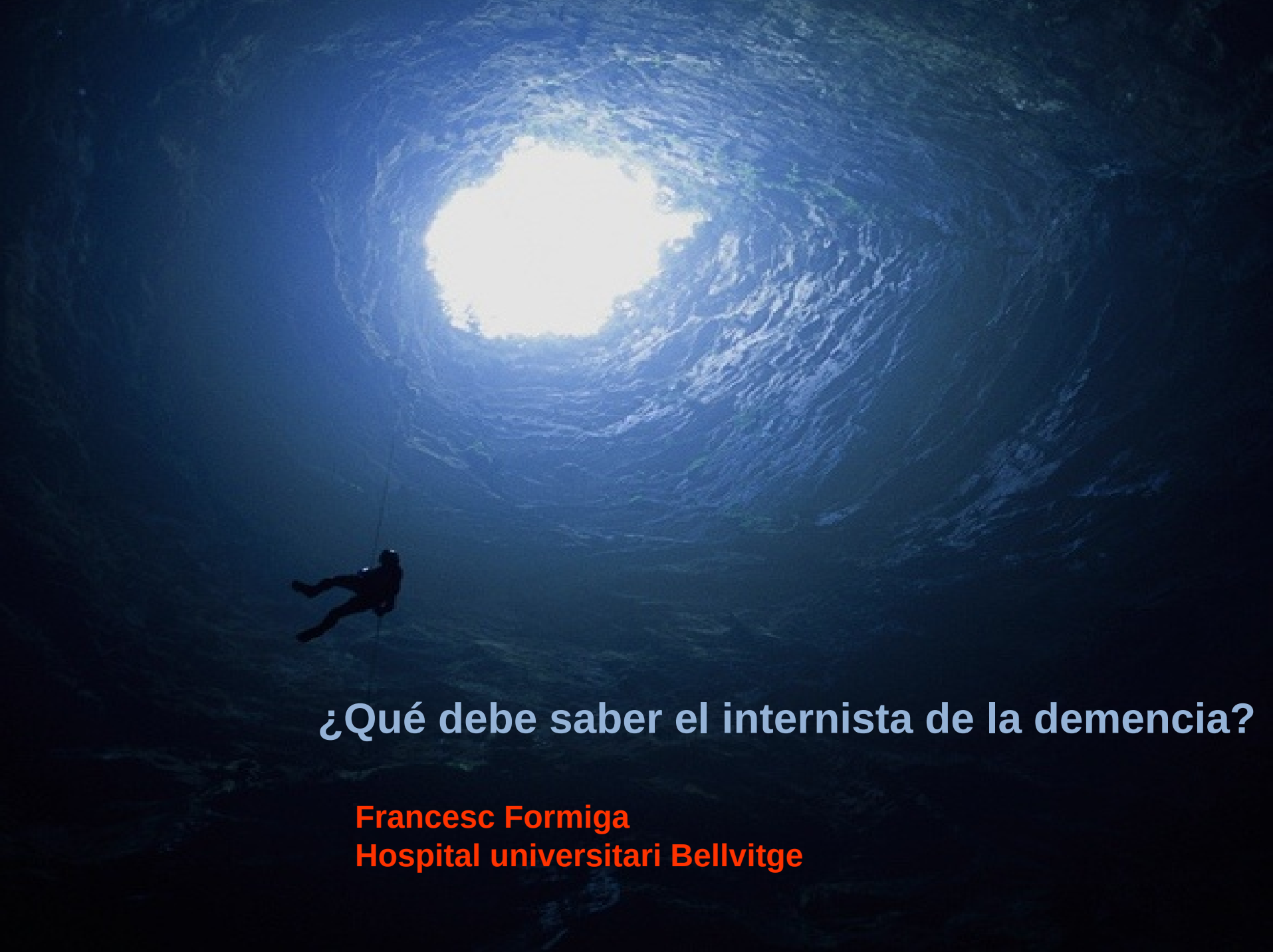


# ¿Qué debe saber el internista de la demencia?

**Francesc Formiga**
**Hospital universitari Bellvitge**

# Prevalencia de la demencia

- **El aumento de la cantidad de pacientes con demencia ira inevitablemente acompañando al aumento del envejecimiento de la población.**

- **La demencia duplica su frecuencia cada 5 años al alcanzar los 60 años de edad.**
- **Demencia un 1-2% población;**
  **5-10% mayores de 65 años;**
  **20-30% mayores de 80 años;**
  **30-40% de los mayores de 85 años.**

Algo más que perdida de memoria ¡¡¡¡¡

# Does This Patient Have Dementia?

Tracey Holsinger, MD
Janie Deveau, MD
Malaz Boustani, MD, MPH
John W. Williams, Jr, MD, MHS

**Context** While as many as 5 million individuals in the United States have dementia, many others have memory complaints. Brief tests to screen for cognitive impairment could help guide dementia diagnosis.

**Objective** To review the literature concerning the practicality and accuracy of brief cognitive screening instruments in primary care.

**Data Sources** A search of MEDLINE (including data from AIDSLINE, BioethicsLine, and HealthSTAR) and psycINFO was conducted from January 2000 through April 2006 to update previous reviews.

**Study Selection** Studies of patients aged 60 years and older and use of an acceptable criterion standard to diagnose dementia were considered.

**Data Extraction** Studies were assessed by 2 independent reviewers for eligibility and quality. A third independent reviewer adjudicated disagreements. Data for likelihood ratios (LRs) were extracted.

**Data Synthesis** Twenty-nine studies using 25 different screening instruments met inclusion criteria; some studies evaluated several different instruments, thus, information could be examined for 38 unique instrument/study combinations.

## CLINICAL SCENARIO

Ms A, an 81-year-old retired nursing instructor who is recently widowed and lives alone, arrives in your office. She is accompanied by her daughter who decided to miss work and attend the appointment because she wanted you to know that her mother has become increasingly forgetful during the past 6 months. The patient is misplacing her glasses and keys more often, and she

# Criterios demencia
# DSM IV

**1.- Deterioro de la memoria a corto y largo plazo: hechos, fechas, datos...**

**2.- Al menos una de las siguientes alteraciones cognitivas:**

- **Afasia (trastorno del lenguaje)**
- **Apraxia (deterioro de la capacidad para llevar a cabo actividades motoras pese a estar intacta la función motora)**
- **Agnosia (fallo en el reconocimiento o identificación de objetos pese a estar intacta la función sensorial)**
- **Alteración de la función ejecutiva (planificación, organización, abstración, funciones viso-espaciales).**

# Criterios demencia
# DSM IV

**3.- Repercusión significativa de estos trastornos en la vida social y/o laboral del paciente.**

**4.- Ha de suponer una merma o declive con respecto a la funcionalidad previa del paciente. Adquirido.**

**5.- Los déficits no aparecen exclusivamente durante un estado de confusión mental, aunque éste puede superponerse a la demencia.**

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

**2011**

## Demencia cualquier tipo

**1.- Repercusión en la vida social y/o laboral del paciente.**

**2.- Declive con respecto a la funcionalidad previa.**

**3.- No se explican por *delirium* o otras alts psiquiátricas.**

**4-Deterioro cognitivo diagnosticado con combinación de historia del paciente o cuidador y valoración objetiva.**

**5-El deterioro cognitivo o conductual abarca un mínimo de dos dominios.**

# Clasificación evolutiva demencias

## REVERSIBLES

- Hidrocefalia normotensiva
- Hipotiroidismo
- Déficit de Vit B12
- Encefalopatía infecciosa
- Hematoma subdural crónico

## IRREVERSIBLES

- Enfermedad de Alzheimer
- Demencia Vascular

# Clasificación etiológica de las demencias

- Enfermedades cerebrales primarias
- Enfermedad de Alzheimer
- Enfermedad de Pick
- Enfermedad por cuerpos de Lewy
- Enfermedad de Parkinson
- Corea de Huntington
- Demencia vascular
- Demencia postraumática
- Hematoma subdural crónico
- Demencia pugilística
- Neoplasias intracraneales
- Hidrocefalia normotensiva
- Enfermedades infecciosas
- Demencia postencefalítica
- Enfermedad de Creutzfeldt-Jakob
- SIDA, Neurolúes

- Encefaloparía hepática, Encf urémica
- Hiper e hiponatremia
- Hipoxia
- Deficiencia de vitamina Bl2-folato
- Pelagra
- Hipo e hipercalcemia
- Hipoglucemia
- Disfunción tiroidea
- Disfunción corticoadrenal
- Enfermedades autoinmunes (LES, vasculitis
- Deficiencia de tiamina (vit. B 1)
- Encefalopatía alcohólica (toxicocarencial)
- Porfiria
- Dependencia a sustancias
- Intoxicación por metales pesados
- Alcoholismo crónico

# Early-onset versus late-onset Alzheimer's disease: the case of the missing *APOE* ε4 allele

*Wiesje M van der Flier, Yolande A L Pijnenburg, Nick C Fox, Philip Scheltens*

*Lancet Neurol* 2011; 10: 280–88

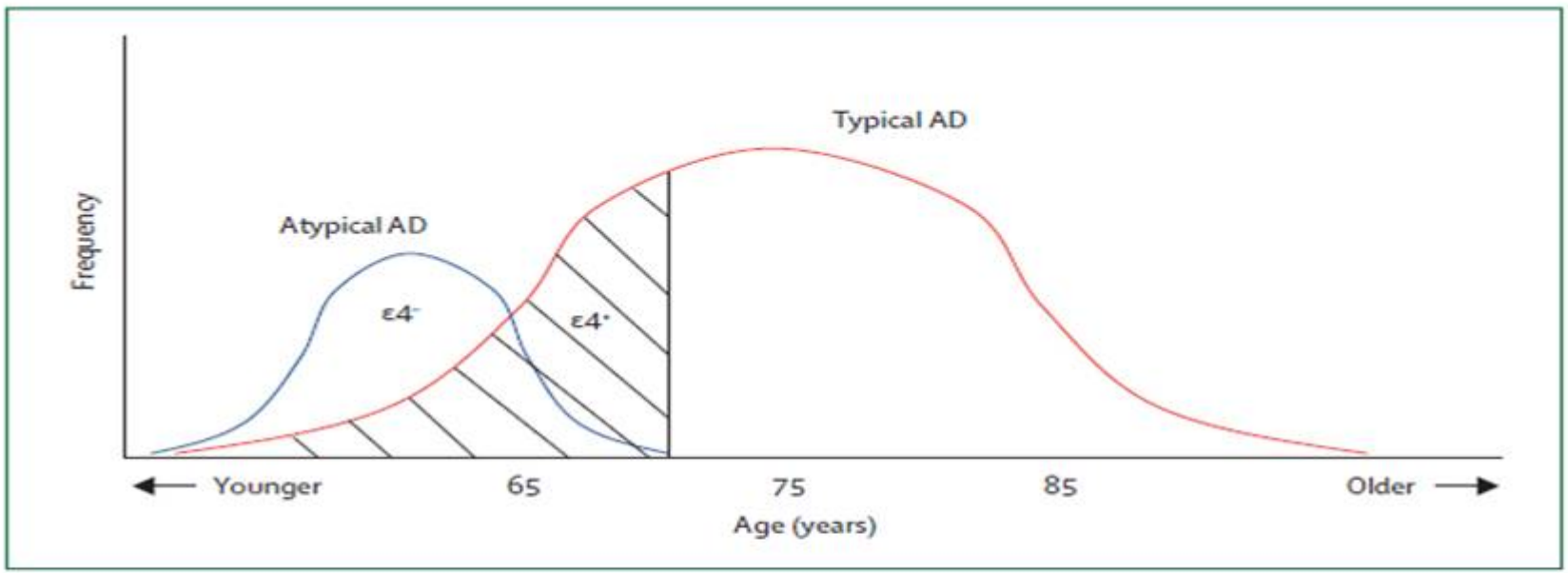



***Figure 2*: Hypothesised frequency distributions of the association between age at onset, absence or presence of *APOE* ε4 allele, and clinical phenotypes of AD**

Most patients have typical AD, which is characterised by prominent memory impairment and hippocampal atrophy, and has an average age at onset of 75 years. The presence of one or two *APOE* ε4 alleles predisposes for this type of disease but is associated with an earlier age at onset (hatched area, roughly 10 years). A smaller group of patients develop Alzheimer's disease at an early age and do not carry the *APOE* ε4 allele. These patients have an atypical clinical presentation of focal cortical, non-memory symptoms, and prominent atrophy in the posterior cortex. AD=Alzheimer's disease.

# Enfermedad de Alzheimer genética (< 5%)

**Patrón autonómico dominante, inicio típicamente presenil.**
**Penetrancia 100%. Las mutaciones son cambios de aminoácidos**

**Factores genéticos** — **Factores ambientales**

**1, 14, 21, 19**

**Depósito amiloide (péptido β)**

**Edad de inicio varia: 20-50 a.**

Oxidación
Inflamación

**Lesión neurona**

**Mutaciones en tres genes:**

**-gen de la proteina precursora amiloide (cromosoma 21)**
**-gen de la presenilina 1 (cromosoma 14)**
**-gen de la presenilina 2 (cromosoma 1)**

| | Role in Alzheimer's disease | Effect on risk of Alzheimer's disease |
|---|---|---|
| **Familial genes** | | |
| *APP* | APP is a membrane protein cleaved by secretases. Cleavage of APP by secretases leads to both non-amyloidogenic processing and production of Aβ. Familial APP mutations result in preferential processing of *APP* through the amyloidogenic pathway[13] | NA |
| *PSEN1* | PSEN1 is a component of α secretase, which is involved in APP processing to Aβ. Familial *PSEN1* mutations can alter the production of $Aβ_{1-42}$ which forms plaques more readily than Aβ1–40[14] | NA |
| *PSEN2* | Processes APP into Aβ as part of the α-secretase complex. Familial mutations can alter the production of Aβ1-42, which forms plaques more readily than $Aβ_{1-40}$[15] | NA |
| *SorL1* | SorL1 interacts with APOE, affects APP trafficking, and overexpression of the protein results in reduced Aβ production. Binding of SorL1 to APP results in reduced Aβ production. SORL1 is a γ-secretase substrate. SorL1 concentrations are reduced in patients with Alzheimer's disease[16] | NA |
| **Risk genes** | | |
| *APOE* | APOE is transported with cholesterol; *APOE* isoforms have differing transport efficiencies. APOE binds Aβ in an isoform-specific manner. APOE is involved in Aβ clearance through interaction with LRP. *APOE4* alleles are associated with increased amyloid burden and cholinergic dysfunction | 3–10 times increased[17] |
| *GSK3β* | GSK3β phosphorylates tau, leading to tangle formation. *APP* cleavage products can activate *GSK3β*, leading to increased tau phosphorylation. GSK3β phosphorylates tau more effectively if tau has already been phosphorylated by other kinases, such as *cdk5*. GSK3β activity can also be promoted by *PSEN* complexes | 1·7 times increased.[18,19] No Alzgene meta-analysis |
| *DYRK1A* | DYRK1A is located on chromosome 21. DYRK1A is involved in tau phosphorylation; its activity is upregulated by Aβ, therefore DYRK1A is a link between amyloid and tau pathologies. *DYRK1A* phosphorylates tau to prime the molecule for further phosphorylation by GSK3β. DYRK1A also phosphorylates septin 4, another tangle protein. DYKR1A is involved in *APP* phosphorylation, which leads to increased amyloidogenic processing through increased BACE interaction | T allele is less frequent in people with Alzheimer's disease. No Alzgene meta-analysis[20] |
| *Tau* | Tau is hyperphosphorylated in NFTs. Tau exists as six splice isoforms depending upon inclusion of N-terminal exons 2 and 3, and the exon 10 microtubule binding domain. Tau mutations can affect splicing and microtubule binding efficacy. The tau haplotype is associated with Alzheimer's disease, and affects expression levels of tau splice isoforms | H1C haplotype more frequent in Alzheimer's disease. No Alzgene meta-analysis of the haplotype[21,22] |
| *TOMM40* | TOMM40 is a translocase of outer mitochondrial membrane 40 homolog on the same chromosome as *APOE*. TOMM40 interacts with APP and is associated with the age of onset in late-onset Alzheimer's disease[23] | Alzgene odds ratio of 0·66 for rs8106922 |
| *CLU* | Clusterin is a chaperone involved in Aβ formation and is associated with severity and progression of Alzheimer's disease[24] | Alzgene odds ratio of 0·87 for rs1113600 |
| *PICALM* | Phosphatidylinositol binding clathrin assembly protein, present in endosomes which are enlarged in early Alzheimer's disease[25] | Alzgene odds ratio of 0·87 for rs541458 |

A full meta-analysis of risk genes can be found on the Alzgene website (http://www.alzgene.org/). NA=not applicable. Aβ=amyloid β. APP=amyloid precursor protein. APOE=apolipoprotein E. NFT=neurofibrillary tangle.

***Table 2:*** **Alzheimer's disease risk genes**

# Enfermedad de Alzheimer esporádica

- **Mayoritaria en la población.**

- **Factores riesgo: envejecimiento, traumatismo craneal, bajo nivel cultural, antecedente familiar de S.de DOWN, antecedentes familiares de EA, factores de riesgo cardiovasculares.**

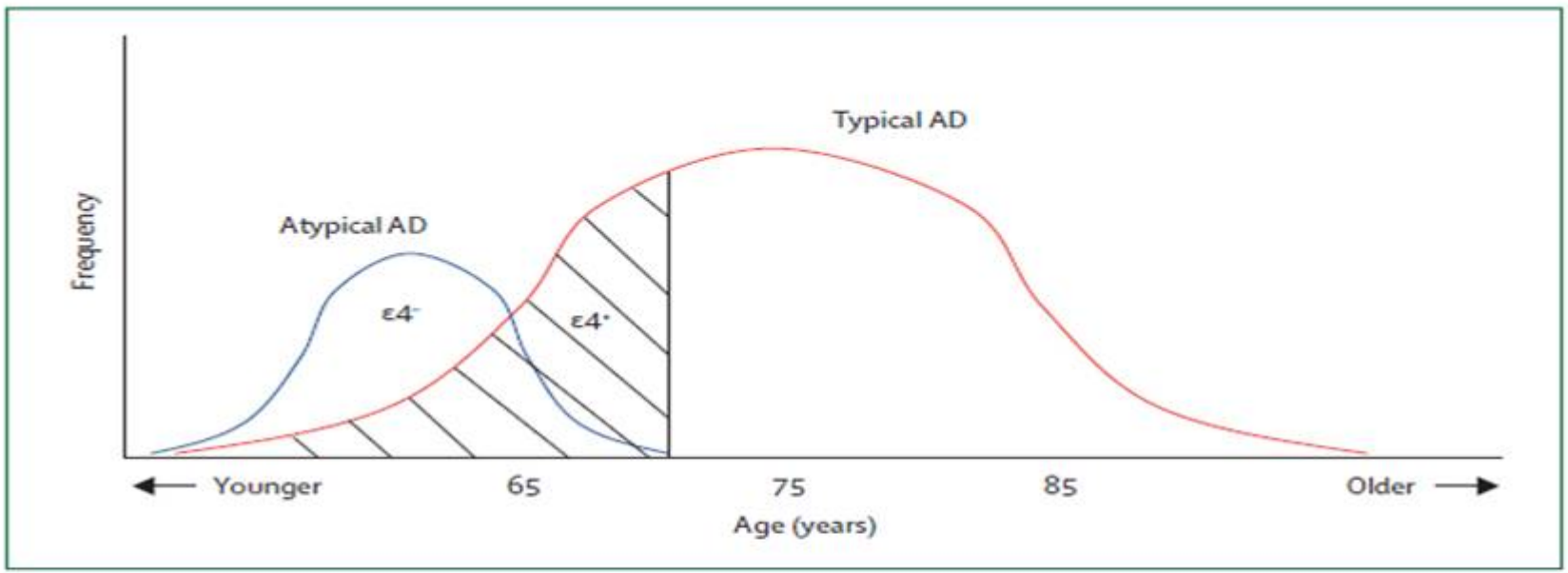
- **Pueden intervenir polimorfismos genéticos de una serie de genes (más de 70) que incrementan la susceptibilidad de sufrir Alzheimer.**

  **El más conocido es el alelo E4 del gen de la apolipoproteina E (cromosoma 19).**

# Early-onset versus late-onset Alzheimer's disease: the case of the missing *APOE* ε4 allele

*Wiesje M van der Flier, Yolande A L Pijnenburg, Nick C Fox, Philip Scheltens*

*Lancet Neurol* 2011; 10: 280–88

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N Engl J Med 2010;362:329-44.

MECHANISMS OF DISEASE

# Alzheimer's Disease

Henry W. Querfurth, M.D., Ph.D., and Frank M. LaFerla, Ph.D.

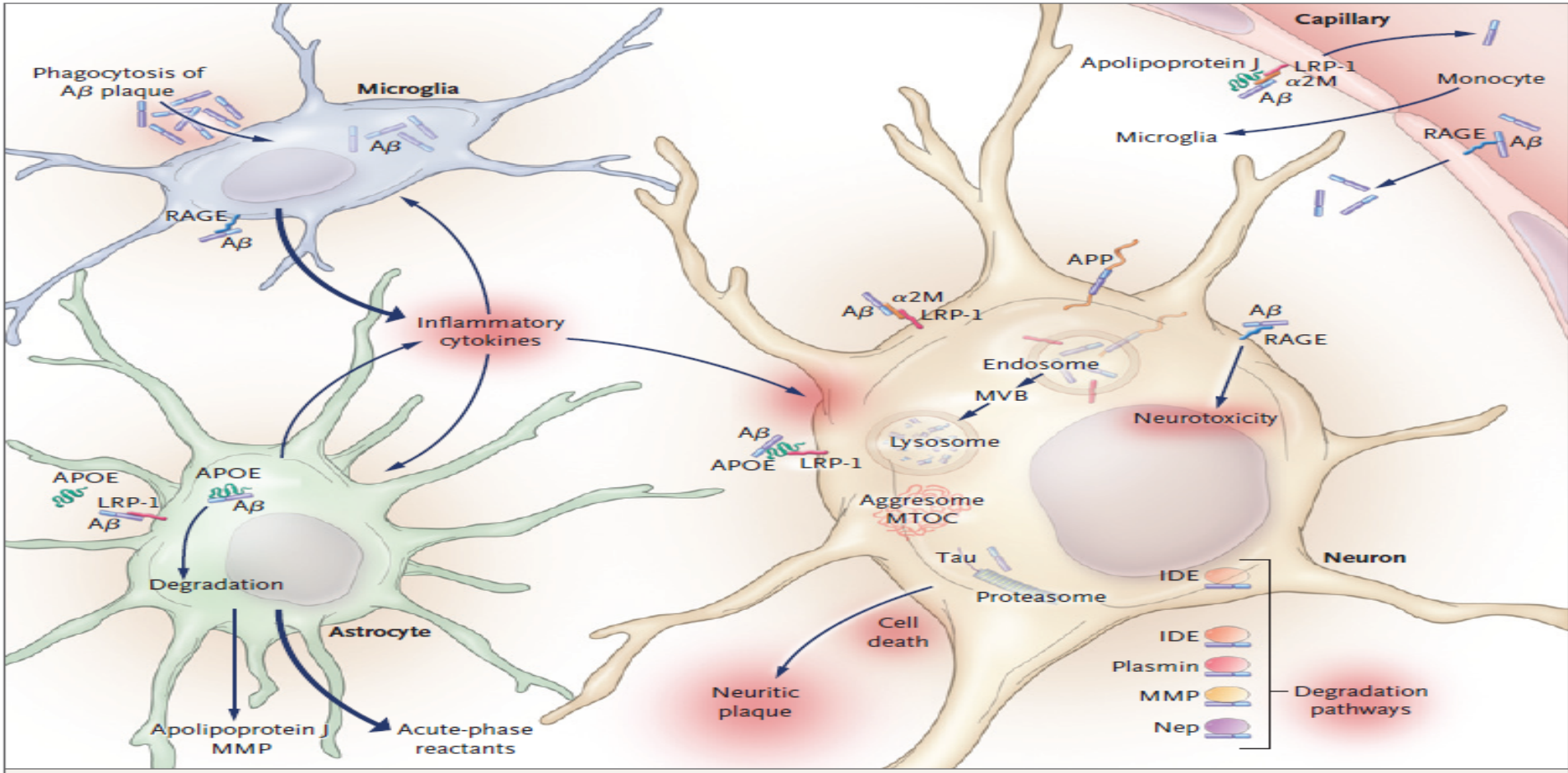



**Figure 5. Inflammation and Mechanisms of Aβ Clearance.**

β-amyloid peptide (Aβ) is formed within intracellular compartments (the endoplasmic reticulum, Golgi apparatus, and endosomes) or it can enter multiple cell types through the low-density lipoprotein receptor–related protein. The ubiquitous apolipoprotein E (APOE) and α2-macroglobulins (α2M) are chaperones in this process and in the genesis of extracellular plaques. Microglia directly engulf Aβ through phagocytosis. Astrocytes also participate in Aβ clearance through receptor-mediated internalization and facilitation of its transfer out of the central nervous system and into the circulation. Microglia and astrocytes are recruited and stimulated in Alzheimer's disease to release proinflammatory cytokines and acute-phase reactants. Receptors for advanced glycation end products (RAGE) molecules transduce extracellular Aβ toxic and inflammatory effects and mediate influx of vascular Aβ. The inflammatory milieu provokes neuritic changes and break-

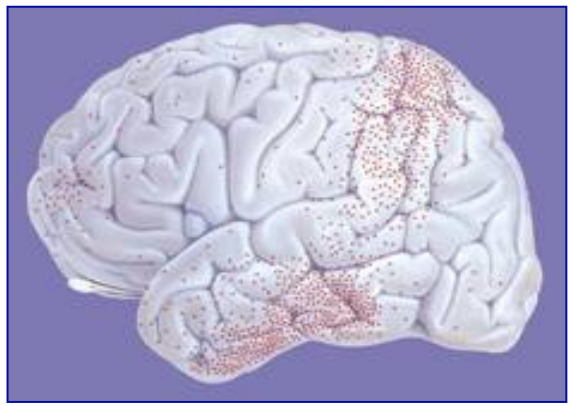
# ENFERMEDAD DE ALZHEIMER

- ***Sustrato neuropatológico:***
  - **Ovillos neurofibrilares**
    - **Agregados de prot. Tau fosforilada**
  - **Placas seniles**
    - **Proteína amiloide insoluble asociada a otras proteínas**
  - **Pérdida neuronal, sináptica, con atrofia y gliosis**
  - **Neuroinflamación**
  - **Compromiso vascular**

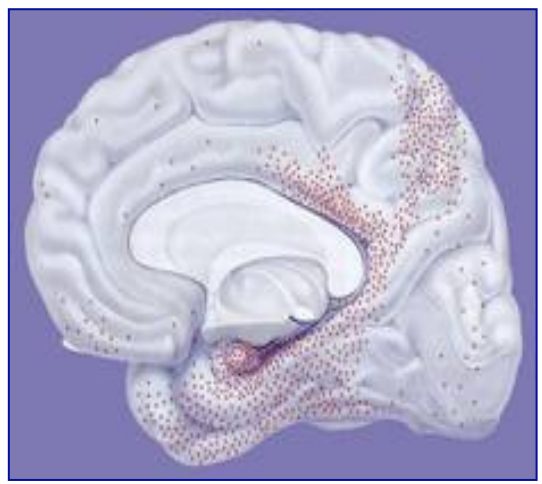
- ***Sustrato neurofisiológico:***
  **Déficit colinérgico (Hipótesis colinérgica).**
  **Se afecta el sistema colinérgico (núcleo de Meynert y su vía colinérgica)**

# Neuropatología

**Los dos tipos de lesiones (placas neuríticas y ovillos neurofibrilares) se pueden encontrar también en el cerebro de ancianos sanos, y lo que en realidad marca el diagnóstico histopatológico es su cantidad y localización, correlacionándose generalmente su número y densidad con la intensidad de la demencia.**



**Patrón de distribución de los ovillos neurofibrilares y placas seniles**



# DIAGNOSTICO DE LA DEMENCIA

- Exploración física completa
- Exploración neurológica completa
- Una exploración con Imagen (TAC,  RM cerebral).
- Laboratorio: Hemograma, P. Bioquimico (glicemia, fx.hepatica, fx. renal, albumina, Ca, Mg), Electrolitos, tiroides, Vit.B12, HIV; VDRL.
- Rx torax, ECG
- A valorar: Ex. Toxicologico (fármacos/drogas)
- Opcional:  Puncion lumbar, SPECT, PET EEG

**El objetivo es DESCARTAR DEMENCIAS SECUNDARIAS.**

**No indicado pruebas genéticas**

# DIAGNOSTICO DE LA DEMENCIA

## Valoración global

- **Escalas de actividades básicas vida diaria (Barthel, Kalz) e instrumentales (Lawton, OARS)**

- **Escalas conductuales (evalúan sintomas no cognitivos): ej. Depresion (Cornell).**

# Nuevos criterios diagnósticos de EA

(Dubois B; Lancet Neurology 2007)

- Nuevos criterios para identificar sujetos en fases precoces, previas a la demencia
- Se basan en el síntoma clínico guía: deterioro de la memoria episódica junto con la presencia de al menos un biomarcador
- Disponibilidad de marcadores fiables
  - RM estructural MRI
  - Neuroimagen molecular con PET
  - LCR

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

**2011**

**Demencia EA: Probable**
**Demencia EA: Probable con aumento del nivel de certeza**
**Demencia EA: Posible**
**Demencia EA: Probable con evidencia de patología asociada a EA**
**Demencia EA: Posible con evidencia de patología asociada a EA**
**Demencia EA: Probada con estudio anatomopatológico**
**Demencia improbable por EA**

# CLASIFICACION SEGUN EL GRADO DE AFECTACION

- **GDS (global deterioration scale)-FAST**
- **Minimental test**
- **Escala de Demencia de Blessed.**
- **Clinical Dementia Rating Scale**

# ESCALA DE REISBERG

| | | |
|---|---|---|
| **GDS 1**<br>**Ausencia de déficit cognitivo** | ⇨ | **(MEC 30-35)**<br>**normal** |
| **GDS 2**<br>**Déficit cognitivo muy leve** | ⇨ | **(MEC 25-30)**<br>**olvido** |
| **GDS 3**<br>**Déficit cognitivo leve.** | ⇨ | **(MEC 20-27)**<br>**deterioro limite** |
| **GDS 4**<br>**Déficit cognitivo moderado** | ⇨ | **(MEC 16-23)**<br>**E.Alzheimer leve** |
| **GDS 5**<br>**Déficit cognitivo moderadamente grave** | ⇨ | **(MEC 10-19)**<br>**E. Alzheimer moderada** |
| **GDS 6**<br>**Déficit cognitivo grave** | ⇨ | **(MEC 0-12)**<br>**E. Alzheimer moderadamente grave** |
| **GDS 7**<br>**Déficit cognitivo muy grave** | ⇨ | **(MEC 0)**<br>**E. Alzheimer grave** |

# *Delirium* y demencia

- **La demencia es un frecuente factor de riesgo de *delirium***
- **El *delirium* es un factor de riesgo de demencia (18-55% desarrollarán demencia 2-3 años)**
- **Debería ponerse en duda el diagnóstico de demencia hasta que hayan pasado de 3 a 6 meses del inicio del *delirium***

**Los ancianos no “se demencian” bruscamente**


Rahkonen T et al. J Neurol Neurosurg Psychiatry 2000; 69: 519-521.

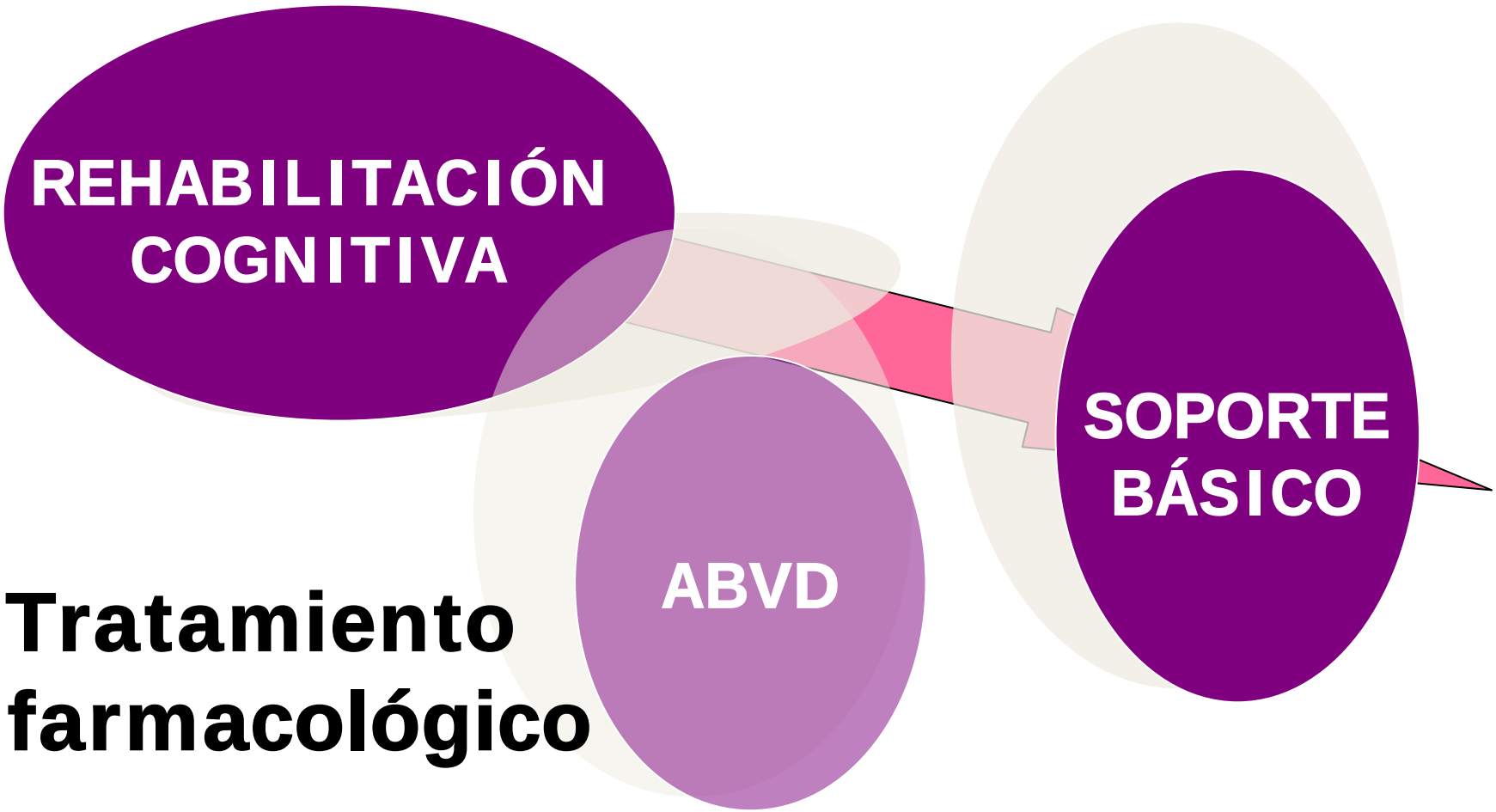
Rockwood K et al. The risk of dementia and death after delirium. Age and Ageing 1999; 28: 551-556.

Fick DM. Superimposed on dementia: a systematic review. JAGS 2002; 50: 1723-32

# Tratamiento de la demencia

- Retrasar la progresión de la enfermedad
- Retrasar el declive funcional
- Mejorar la calidad de vida
- Apoyar y mantener la dignidad del paciente
- Controlar los síntomas

# TRATAMIENTO GLOBAL




**Tratamiento farmacológico**

# Tratamiento específico

- **Existe evidencia científica que avala la *eficacia y seguridad del tratamiento específico* en pacientes ancianos afectos de enfermedad de Alzheimer (EA) no sólo en la esfera cognitiva si no también para prevenir y tratar los SCPD, retrasar el declive funcional y disminuir la necesidad de horas y sobrecarga del cuidador, retrasando la institucionalización.**

*Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D et al. Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline. Ann Intern Med. 2008;148:379-397.*

# TRATAMIENTO ESPECÍFICO

- HIPOTESIS COLINERGICA

**Existe un déficit de acetilcolina en la neurotransmisióm en la EA**

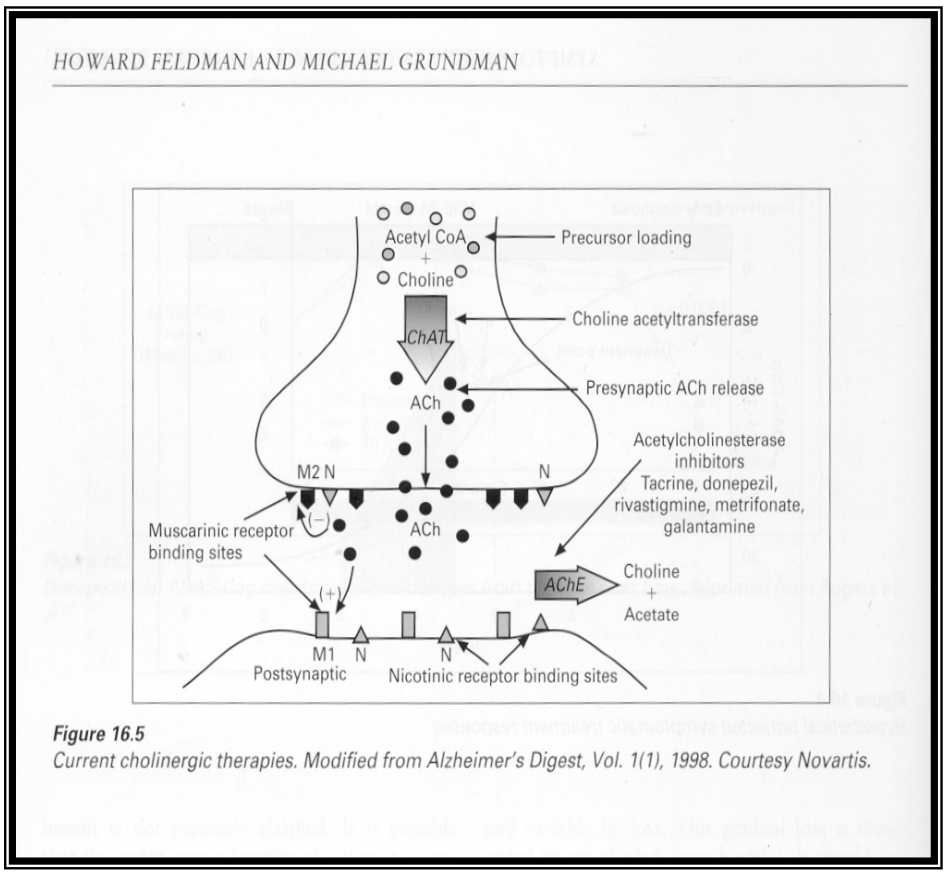



*Figure 16.5*
*Current cholinergic therapies. Modified from Alzheimer's Digest, Vol. 1(1), 1998. Courtesy Novartis.*

- INHIBIDORES DE LA ACETILCOLINESTERASA:

**Inhiben la degradación de la acetilcolina a nivel del espacio sináptico.**

- ✓ **Donepezilo**
- ✓ **Rivastigmina**
- ✓ **Galantamina**

- **REQUISITOS**
- ✓ **MMSE 10-24**
- ✓ **GDS 3- 4-5-6**

# TRATAMIENTO ESPECÍFICO

## MEMANTINA

- **Antagonista no competitivo del receptor NMDA del glutamato.**
- **Impide la neurotoxicidad que provoca el exceso crónico de glutamato y por otra promueve su actividad fisiológica en el receptor NMDA.**
- **Indicado en la EA fase moderada o severa.**
- **Dosis 20 mg/24 h.**
- **Bien tolerada.**

**REQUISITOS**

**MMSE 3-20**

**GDS 4, 5, 6, 7a**

# TRACTAMENTO COMBINADO

## ANTICOLINESTERÁSICOS + MEMANTINA

- fases moderadas y moderadamente graves
  - ✓ **MMSE: 20-10**
  - ✓ **GDS 4-6**
  - ✓ **Tienen mecanismos de acción diferente**
  - ✓ **No hay interacciones entre los dos fármacos**
  - ✓ **Eficacia demostrada del tratamiento combinado**

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2010;29:198–203
DOI: 10.1159/000278348

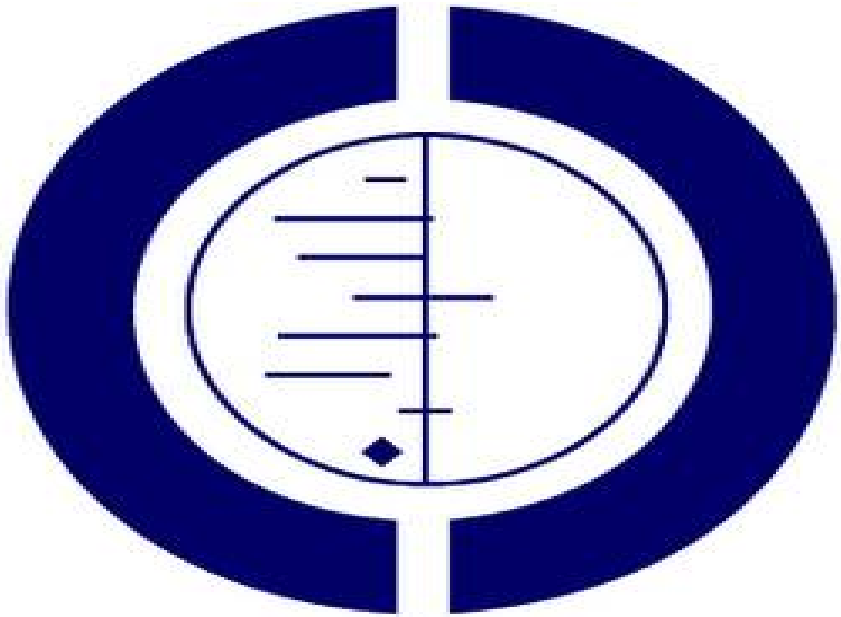
Accepted: January 14, 2010
Published online: March 20, 2010

# Lower Barthel Index Scores Predict Less Prescription of Pharmacological Therapy in Elderly Patients with Alzheimer Disease

Francesc Formiga[a] Isabel Fort[b] Maria Jose Robles[c] Daniel Rodriguez[d]
Pedro Regalado[e]

**Nunca la edad debe ser el criterio para no recibir Tratamiento especifico para la EA.**

**VALORACION GERIATRICA GLOBAL**



THE COCHRANE
COLLABORATION®

# Donepezilo

THE COCHRANE COLLABORATION®

[Intervention Review]

## Donepezil for dementia due to Alzheimer's disease

Citation: Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD001190. DOI: 10.1002/14651858.CD001190.pub2.

**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2009.

**Mejora significativa en la cognición (incluido a 52 semanas), en las actividades de la vida diaria y reducción en el riesgo de declive funcional comparado con placebo.**

**Mejor dosis 10mg pero más efectos secundarios.**

# Rivastigmina

THE COCHRANE COLLABORATION®

[Intervention Review]

## Rivastigmine for Alzheimer's disease

Citation: Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD001191. DOI: 10.1002/14651858.CD001191.pub2.

**Publication status and date:** Edited (no change to conclusions), published in Issue 3, 2009.

**Beneficio modesto para la rivastigmina a dosis altas sobre la cognición y actividades de la vida diaria.**

**Efectos secundarios frecuentes que se pueden disminuir con la presentación en parche.**

# Galantamina

THE COCHRANE COLLABORATION®

[Intervention Review]

## Galantamine for Alzheimer's disease and mild cognitive impairment

Citation: Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD001747. DOI: 10.1002/14651858.CD001747.pub3.

**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2009.

**En pacientes con EA leve-moderada galantamina fue más efectiva que el placebo para mejorar la función cognitiva y los síntomas generales con dosis de 16 mg/día o mayores.**

**Se ha descrito mejoría discreta en las medidas de las actividades de la vida diaria y los síntomas conductuales**

# Memantina

THE COCHRANE COLLABORATION®

[Intervention Review]

## Memantine for dementia

Citation: McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub5.

**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2009.

**En pacientes con EA moderada a grave tras 6 meses de tratamiento, se observó una beneficio estadísticamente significativo en la valoración de los distintos aspecto de eficacia que favoreció a memantina al final de seguimiento en la función cognitiva, la impresión clínica de cambio, en las actividades de la vida diaria y en el estado de ánimo y conducta (menor agitación). BIEN TOLERADO**

Drugs Aging 2011; 28 (7): 539-546
1170-229X/11/0007-0539/$49.95/0



# Combination Therapy for Alzheimer's Disease

Overall, CT in AD seems to be safe and well tolerated, and may represent the current gold standard for treatment of moderate to severe AD and possibly mild to moderate AD as well. Unfortunately, major stumbling blocks to recommending CT in AD appear to be cost and a therapeutically nihilistic attitude among many practitioners that current AD therapies are not worth prescribing. The authors, based on evidence presented in this review as well as their own clinical experience, strongly support the use of CT in AD.

# ¿Alguno de los IACE es mejor que otro?

THE COCHRANE COLLABORATION®

## Cholinesterase inhibitors for Alzheimer's disease (Review)

Citation: Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD005593. DOI: 10.1002/14651858.CD005593.

**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2009.

**No se observaron diferencias estadísticamente significativas.**

**EC abiertos. Pocos pacientes incluidos, duración variable (12-52s).**

**Promotor industria: resultados a favor del fármaco del promotor. Valoración con escalas no validadas.**

Review Articles | Alzheimer's & Dementia 7 (2011) 177–184

# Defining optimal treatment with cholinesterase inhibitors in Alzheimer's disease

Gary Small[a*], Roger Bullock[b]

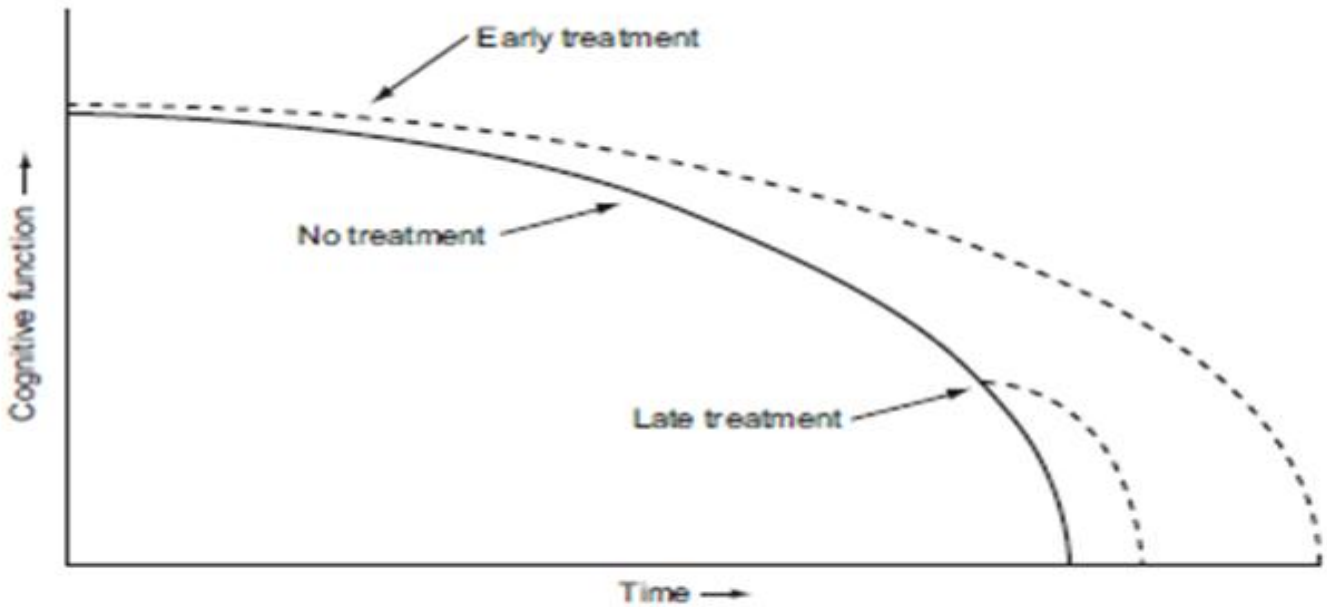



Fig. 1. Predicted effect of early versus late treatment of AD.

Review Articles | Alzheimer's & Dementia 7 (2011) 177–184

# Defining optimal treatment with cholinesterase inhibitors in Alzheimer's disease

Gary Small[a*], Roger Bullock[b]

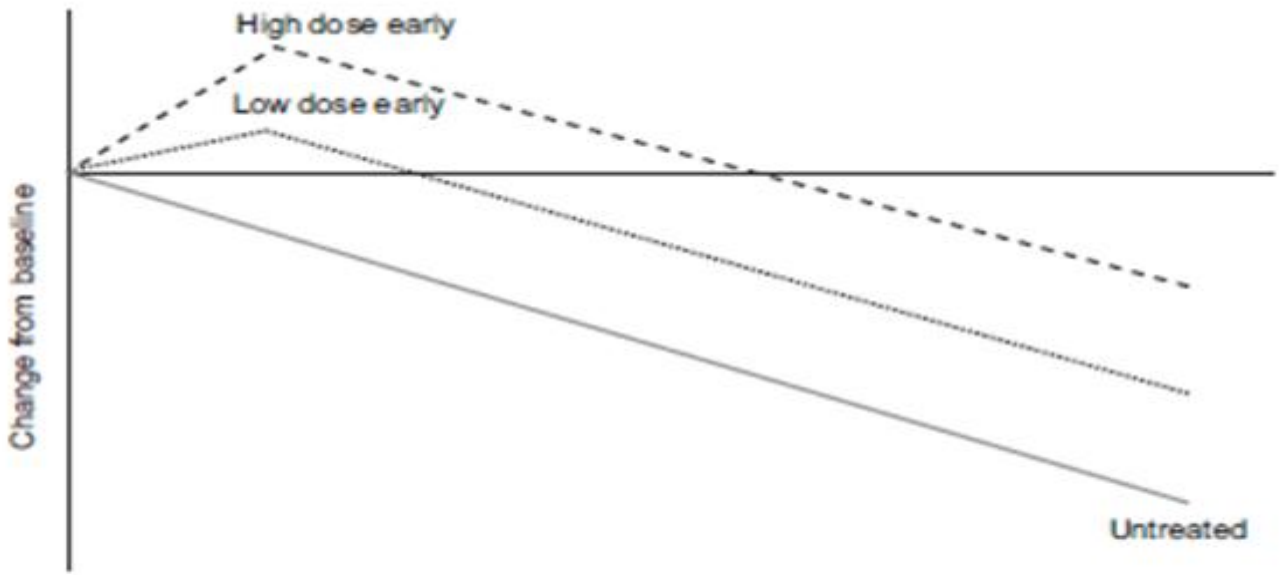



Fig. 4. Potential of high-dose cholinesterase inhibition early as an approach to prolong the mild disease stage for as long as possible (schematic representation of theoretical response).

# Alzheimer's Disease: Future Treatments

DOI:10.1016/j.jamda.2010.10.008

John E. Morley, MB, BCh

**Table 1.** *Therapies That Are Being Developed for Alzheimer's Disease*

Acetylcholinesterase Inhibitors
- Donepezil
- Rivastigmine (available as tablets and patch)
- Galantamine

NMDA Receptor Antagonists
- Memantine

Preventing Production of Amyloid-beta production
- Antisenses to amyloid precursor protein
- Anti-beta-secretase antibodies
- Modulating gamma-secretase production
- Immunization

Increasing Amyloid-beta Protein Clearance
- Passive anti-amyloid beta antibodies

Preventing Amyloid-beta Protein Aggregation

Decreasing Tau Aggregation
- Valproic acid
- Methylene blue

Reversing Mitochondrial Dysfunction
- Alpha-lipoic acid
- Latrepiridine

Other Treatments
- Testosterone in males
- Nerve growth factor
- Phosphodiesterase 9A inhibitors
- Docasahexanoic acid
- Other nutrients

Clinical Therapeutics/Volume 32, Number 3, 2010

# Systematic Reviews of Assessment Measures and Pharmacologic Treatments for Agitation

Scott L. Zeller, MD[1]; and Robert W. Rhoades, PhD[2]

*[1]Alameda County Medical Center, Oakland, California; and [2]Steamboat Springs, Colorado*

**Results:** The literature search identified 13 scales used to assess the severity of agitation across multiple patient populations; only 3 of these reports involved the prediction of aggression/violence in patients with agitation, and 1 involved prediction of the need for medication. Thirty-one clinical trials of pharmacotherapy for agitation were identified by the literature search. Based on their results, orally administered olanzapine, risperidone, aripiprazole, quetiapine, haloperidol, and lorazepam; intramuscularly administered olanzapine, lorazepam, ziprasidone, haloperidol, aripiprazole, midazolam, and droperidol; and intravenously administered droperidol and lorazepam were effective for the treatment of agitation. The intramuscular route of administration was associated with a more rapid onset of action compared with the oral route (eg, for olanzapine, 30 minutes vs 1 hour, respectively).

**Tratamiento SCAD**

# Aspectos de comorbilidad en pacientes ancianos con demencia. Diferencias por edad y género

F. Formiga[a], I. Fort[b], M. J. Robles[c], E. Barranco[d], M. C. Espinosa[e] y S. Riu[f], del Grupo de trabajo de demencia de la Sociedad Catalana de Geriatría y Gerontología

*Rev Clin Esp.* 2007;207(10):495-500

*Fundamento y objetivo.* La prevalencia de demencia en pacientes ancianos es alta. El objetivo del estudio es evaluar algunos aspectos de comorbilidad en los pacientes con demencia. Además se explora si existen diferencias según la edad (mayores o no de 84 años) y el género de los pacientes.

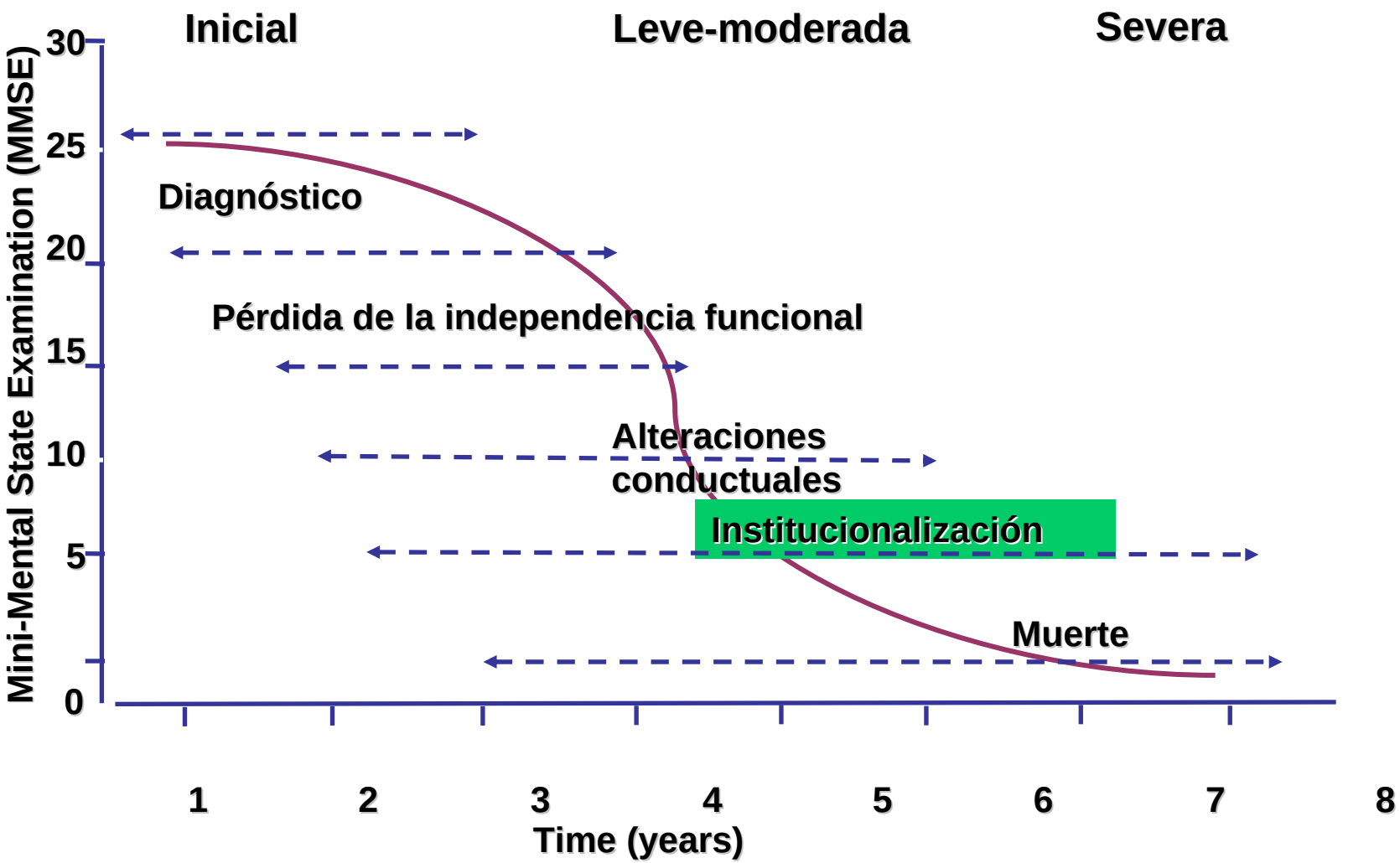
*Pacientes y métodos.* Se evaluaron prospectivamente 311 pacientes mayores de 64 años con demencia. Se recogieron variables sociodemográficas, el tipo de demencia, el índice de Barthel (IB), el índice de Lawton (IL), el *Mini Mental State Examination* (MMSE), el índice de Charlson, el número total de medicamentos, los antecedentes de hipertensión (HTA), diabetes (DM), dislipidemia (DL), insuficiencia cardíaca (IC), enfermedad pulmonar obstructiva crónica (EPOC) y neoplasia.

***Resultados.*** **Se trataba de 222 mujeres (71,4%) y 89 varones, con una edad media (desviación estándar [DE]) de 80,6 (6) años. La media del número total de medicamentos fue de 5,8 (2,6). La media del índice de Charlson fue de 2,1 (1,3). Existía en el 51% de los casos HTA, en 24% DM, en 24% DL, en 13% IC, en 11% EPOC y en el 8% neoplasia. Respecto al género, destacaba mejor puntuación en el MMSE, mayor comorbilidad, mayor porcentaje de casados y mayor prevalencia de demencia vascular en hombres en comparación con las mujeres, donde había mayor presencia de enfermedad de Alzheimer y mayor porcentaje de viudas. En relación a la edad había mayor número de viudos, peor IL, más IC y menos DL en los mayores de 84 años.**

***Conclusiones.*** **Los pacientes ancianos con demencia tienen una alta comorbilidad y un importante consumo de fármacos de prescripción crónica. Existen variaciones en la comorbilidad según la edad y el género, que deben tenerse en cuenta.**

**IMPORTANTE COMORBILIDAD**

# Historia natural de la EA



# Mortalidad en la demencia

**Annals of Internal Medicine** 2004;140:501-509. | ARTICLE

## Survival after Initial Diagnosis of Alzheimer Disease

Eric B. Larson, MD, MPH; Marie-Florence Shadlen, MD; Li Wang, MS; Wayne C. McCormick, MD, MPH; James D. Bowen, MD; Linda Teri, PhD; and Walter A. Kukull, PhD

- **Se evalúan 521 pacientes con enfermedad de Alzheimer de debut.**
- **La media de supervivencia fue 4,2 años para los hombres y 5,7 años para las mujeres, menor que la esperada por su edad.**


Demencia terminal

- **Es difícil identificar cuando los pacientes con enfermedades crónicas pasan a ser pacientes en fase terminal.**

- **El porcentaje de error pronostico (supervivencia mayor de 180 días) al estudiar 6451 pacientes tras ser incluidos en un programa de paliativos era del 15%:**

  **-oncológicos 12%**

  **-insuficiencia cardíaca 22%**

  **-EPOC 32%**

  -demencia 35%

*Christakis NA. Survival of Medicare Patients after enrollement in hospice programs. N Engl J Med 1996; 335: 172-8.*

**Recomendaciones para una correcta toma de decisiones.**

**Ordenes de limitación de actuaciones en la historia clínica.**

International Psychogeriatrics (2011), 23:4, 539–545 © International Psychogeriatric Association 2010
doi:10.1017/S1041610210001535

# Discontinuing cholinesterase inhibitors: results of a survey of Canadian dementia experts

Table 1. Recommendations for discontinuing cholinesterase inhibitors after long-term use

**A) Consider discontinuation if:**

1. patient/caregiver prefers to discontinue and they have been appraised of all the risks and benefits of continuation and discontinuation;
2. rate of cognitive, functional, and/or behavioral decline is greater on treatment compared to prior to being treated;
3. Global Deterioration Scale (GDS) = 7;
4. when patient experiences swallowing difficulties;
5. if patient develops significant gastrointestinal adverse events (nausea, vomiting, distressing loose stools, anorexia with weight loss).

**B) Do not necessarily consider discontinuation:**

1. based on MMSE score alone;
2. when a patient is institutionalized;
3. based on adverse events that have multiple potential etiologies (e.g. falls).

Drugs Aging 2010; 27 (6): 435-449
1170-229X/10/0006-0435/$49.95/0



# Withholding, Discontinuing and Withdrawing Medications in Dementia Patients at the End of Life

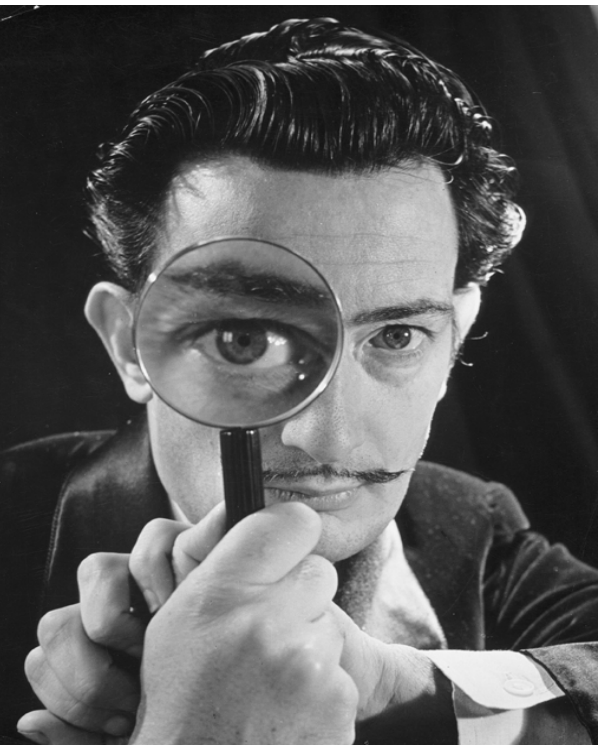
## A Neglected Problem in the Disadvantaged Dying?

Recent years have seen a growing recognition that dementia is a terminal illness and that patients with advanced dementia nearing the end of life do not currently receive adequate palliative care. However, research into palliative care for these patients has thus far been limited. Furthermore, there has been little discussion in the literature regarding medication use in patients with advanced dementia who are nearing the end of life, and discontinuation of medication has not been well studied despite its potential to reduce the burden on the patient and to improve quality of life. There is limited, and sometimes contradictory, evidence available in the literature to guide evidence-based discontinuation of drugs such as acetylcholinesterase inhibitors, antipsychotic agents, HMG-CoA reductase inhibitors (statins), antibacterials, antihypertensives, antihyperglycaemic drugs and anticoagulants. Furthermore, end-of-life care of patients with advanced dementia may be complicated by difficulties in accurately estimating life expectancy, ethical considerations regarding withholding or withdrawing treatment, and the wishes of the patient and/or their family. Significant research must be undertaken in the area of medication discontinuation in patients with advanced dementia nearing the end of life to determine how physicians currently decide whether medications should be discontinued, and also to develop the evidence base and provide guidance on systematic medication discontinuation.

Demencia es un problema MUY frecuente

NECESARIO ESTAR CAPACITADO
-Para diagnóstico y tto especifico

INCORPORAR HABILIDADES
-Para tto comorbilidad
-Para ayuda final de la vida



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**Muchas Graciasˡ¡¡**