52° Congresso Nazionale SIGG
Firenze, 28 novembre-2 dicembre 2007
Simposio: "Ci sono novità nell'Alzheimer?"

Novità terapeutiche e nuove vie di somministrazione dei farmaci per la demenza

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A century of Alzheimer's disease

- In November 1901, Alzheimer admitted Auguste D., a 51-year-old patient, to the Frankfurt hospital
- Death of Auguste D, April 8th, 1906
- On 3rd November 1906, at the 37th meeting of the Society of Southwest German Psychiatrists in Tübingen, Alzheimer presented the clinical and neuropathological features of the disease that Kraepelin subsequently named after him.
- 1910: Krapelin uses the term "Malattia di Alzheimer" in:Psychiatrie: Ein Lehrbuch für Studierende und Arzte. Leipzig:Barth, 1910:593-632.

Has the management of Alzheimer's disease changed over the past 100 years?

Konrad Maurer, Ian McKeith, Jeffrey Cummings, David Ames, Alistair Burns

Lancet 2006; 368: 1619–21

In February 1902 Auguste D suffered from constant restlessness and anxious confusion. She approached each day with such a negative attitude that examining her became impossible. Consequently, she spent the entire day, and often the evening in the bath. At night she was usually put in an isolation room because she could not fall asleep in the main ward; she went to other patients' beds and woke them. In a private room, after a longer or shorter period of persistent wandering about, she fell asleep. Alzheimer noted that she would never lie properly in her bed and did not use the bedding correctly. She covered herself with pillows and huddled on the feather quilt.

Alzheimer developed the treatment plan himself. Initial treatment for insomnia was dietary. For patients with chronic illnesses and those with strong constitutions, extensive outdoor activity, exercise and massage were prescribed, but strenuous physical exertions can cause sleeplessness in those who are easily excited or have recently become ill. For such patients, extended lukewarm baths (balneotherapy) with simultaneous cooling of the head and moist wrappings were preferred. Alzheimer had done extensive work on the therapeutic value of warm and mild baths that extend over several hours, even days, and soothe agitated patients. Treating the head with weak electrical currents (galvanization) seemed appropriate to the physicians in some cases, as did hypnotic suggestion. Often patients showed great improvement with the introduction of afternoon rest, light, early dinners, the avoidance of reading in the evening, abstention from tea and coffee, evening bowel evacuations, regular bedtimes and extensive airing of the bedroom.

Alcohol was administered in mild doses. The doctors used sedatives only in emergencies—in cases of great fear or acute pain, for example—because it is difficult to reaccustom patients to natural sleep. In cases of extreme agitation refractory to other means, when rapid calming was necessary, chloroform was used.

In the treatment of Auguste D and many other troubled patients, sedatives were very useful. Such patients were given 2 to 3 grams of chloral hydrate, a sedative that induced a longer-lasting, restful sleep. If the patient could not tolerate chloral hydrate, paraldehyde, an unpleasant-smelling and -tasting colourless liquid developed in 1883, could be administered. In small doses of 5 grams—which one can safely increase two- or threefold—it effects a long, deep, restful sleep, akin to natural sleep.

Amylene hydrate had certain advantages over paraldehyde: later sulphonal, tetronal and somnol were used. The legendary Veronal (barbital), a barbituric acid preparation developed by Merck and Bayer, was still being tested on animals at this time and was not made available for patients for several years*.

Impact of Alzheimer's Disease

- Most common form of dementia
  - 10% of people aged 65–69 yrs
  - 50% of people over 85 yrs
- Caregiver burden
  - Spend a range of 13–81 hours weekly providing care
  - Are 2–3 times more likely to be depressed vs non-caregivers
  - Have 46% more physician visits than non-caregivers
  - Have 71% greater use of prescription medication vs non-caregivers

Alzheimer's Association Website: http://www.alz.org/AboutAD/statistics.asp
Family Caregiver Alliance Website: http://www.caregiver.org/caregiver/jsp

100 Years and Counting: Prospects for Defeating Alzheimer's Disease

Erik D. Roberson and Lennart Mucke*

- It used to be said that *neurologic diseases were easy to diagnose but impossible to treat.* Today, effective treatments are available for many neurologic conditions, but for the 4.6 million new patients worldwide who will be affected by AD this year, the old mantra still rings too true.
- Although multiple drugs have now been approved, their expected benefits are modest. One hundred years after the discovery of AD, the lack of treatments with a major impact might be discouraging. Fortunately, basic research is identifying many of the pathways that contribute to this devastating disease, providing unprecedented opportunities for the development of new treatments aimed at the root causes of AD.

www.sciencemag.org SCIENCE VOL 314 3 NOVEMBER 2006

- a delay in onset of AD by 5 years would reduce the overall prevalence of 50% whereas a delay of 10 years would produce a 75% reduction.

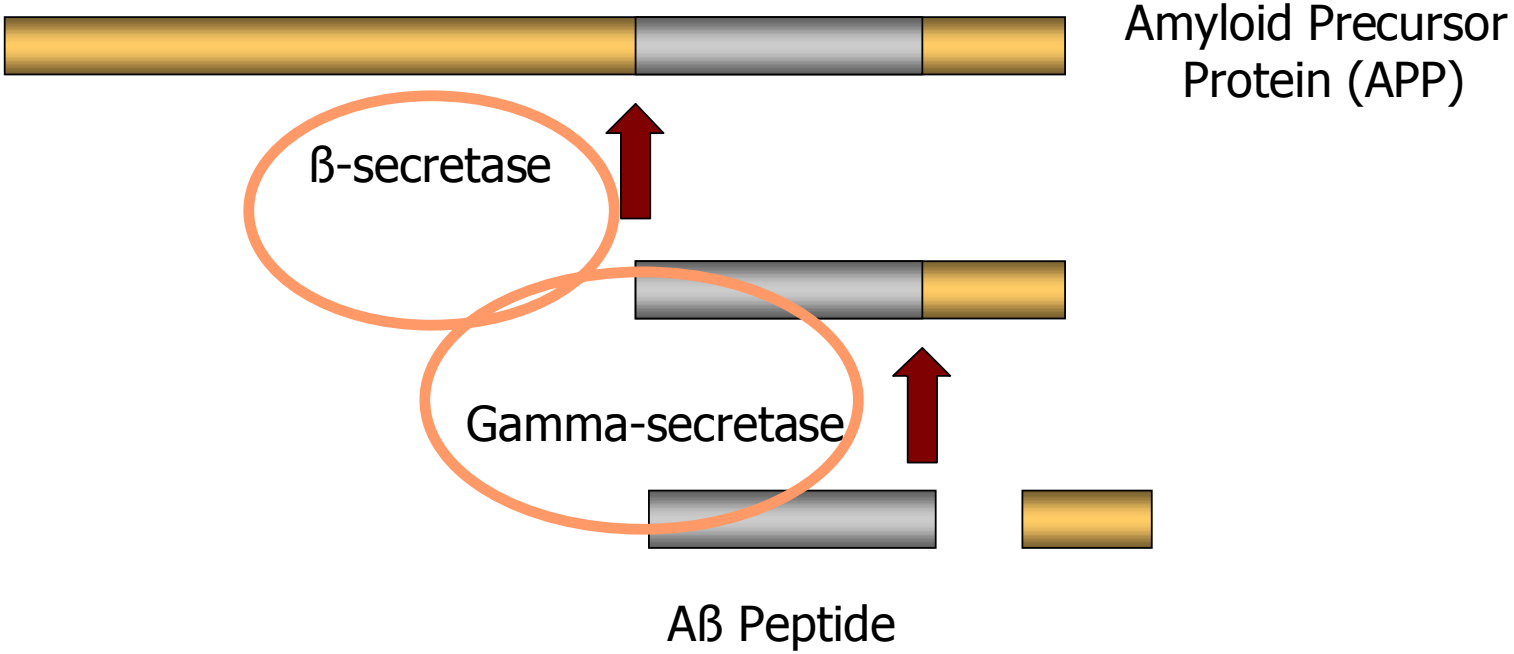
Thal J et al, Alzheimer Dis Assoc Disord 1997

Future Disease-modifying Therapies

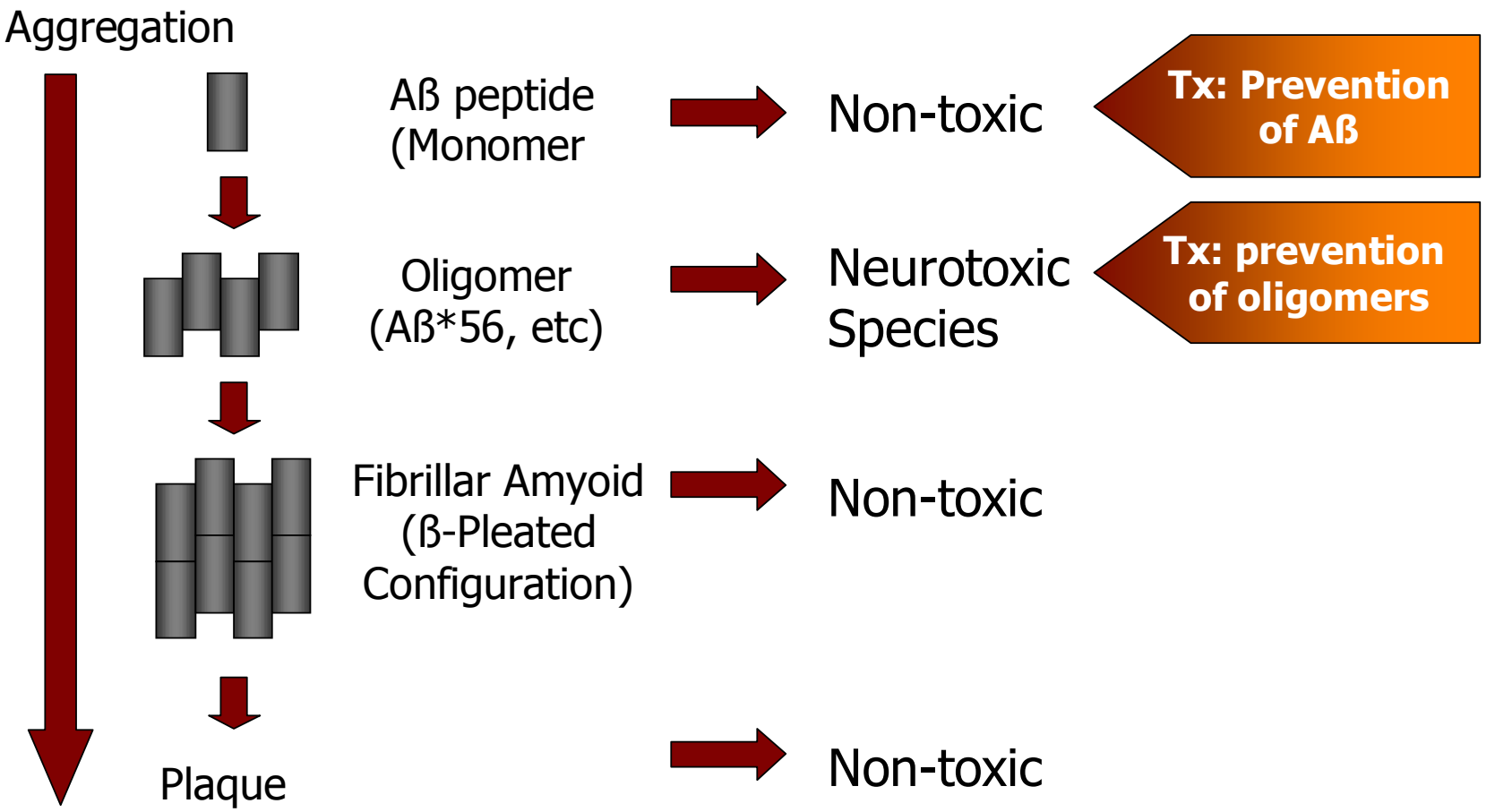
- Antiamyloid agents
  - Affect toxicity associated with Aβ peptide
- Neuroprotective agents
  - Reduce injury from abnormal amyloid protein processing
    - Antioxidants
    - Tau-related therapies
    - Nerve growth factors and promoters
    - Anti-inflammatory agents
    - Myelin preservation agents
- Neurorestorative approaches
  - Neurotrophic and nerve growth factor strategies
  - Transplantations
  - Stem-cell related interventions

Cummings JL, Neurology 2007

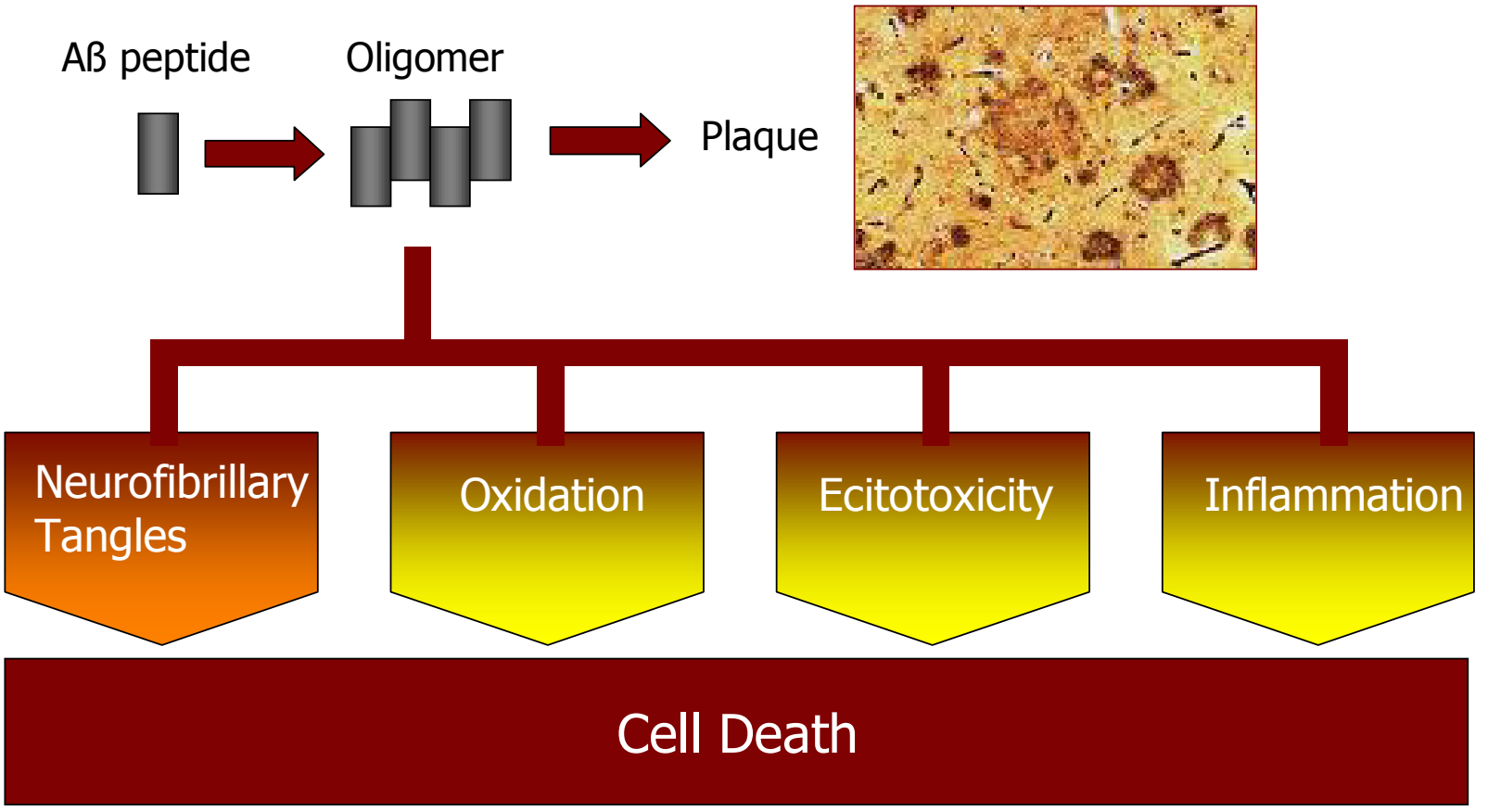
APP Processing Offers Opportunities of Therapeutic Intervention



The Amyloid Hypothesis Has Been Transformed into the Amyloid Oligomer Hypothesis



Amyloid Oligomers Initate a Cascade of Cytotoxic Events



HIGH LIGHT

Effects of a γ-secretase inhibitor in a randomized study of patients with Alzheimer disease

Abstract—LY450139 dihydrate, a γ-secretase inhibitor, was studied in a randomized, controlled trial of 70 patients with Alzheimer disease. Subjects were given 30 mg for 1 week followed by 40 mg for 5 weeks. Treatment was well tolerated. $A\beta_{1\text{-}40}$ in plasma decreased by 38.2%; in CSF, $A\beta_{1\text{-}40}$ decreased by $4.42 \pm 9.55\%$ (p = not significant). Higher drug doses may result in additional decreases in plasma Aβ concentrations and a measurable decrease in CSF Aβ.

NEUROLOGY 2006;66:602–604

E.R. Siemers, MD; J.F. Quinn, MD; J. Kaye, MD; M.R. Farlow, MD; A. Porsteinsson, MD; P. Tariot, MD; P. Zoulnouni, MD; J.E. Galvin, MD; D.M. Holtzman, MD; D.S. Knopman, MD; J. Satterwhite, PhD; C. Gonzales; R.A. Dean, MD, PhD; and P.C. May, PhD

- LY450139 was well tolerated and reduced amount of Aβ in the plasma but not in CSF

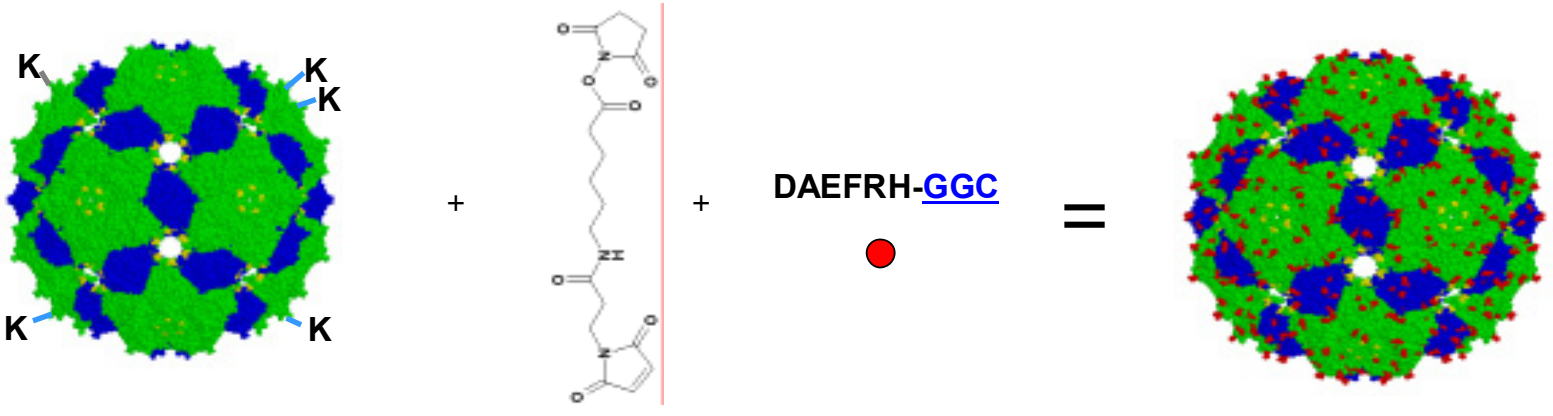
- The potential for dose escalation is limited because γ-secretase also cleaves other substrates, including Notch and non-selective γ-secretase have deleterious effects on embryogenesis in zebrafish and on lymphoid and gastrointestinal tissues in mammals

Aβ immunotherapy

- Active immunisation of AD transgenic mice with fibrillar Aβ attenuated Aβ deposition (*Nature 1999*)
- Similar results by passive immunisation with antibodies against Aβ. Effect could be mediated by anti-Aβ antibodies that bind to Aβ plaques and induce Aβ clearance by microglia, or alternatively bind soluble Aβ in the periphery, thereby driving an Aβ efflux from the brain (*Nat Med 2000*)
- Results were the basis for clinical trials with **active immunisation with the vaccine AN1792, composed of pre-aggregated Aβ42**. However, the phase IIa AN1792 trial had to be interrupted because **6% of cases developed encephalitis**.
- The 2nd generation of immunotherapy, Aβ immunoconjugates composed of the N-terminal part of Aβ conjugated to a carrier protein, could allow for active immunisation with reduced risk of TH-1 mediated side-effects. **Both active immunisation** with N-terminal Aβ fragments **and passive immunisation** with humanised anti-Aβ monoclonal antibodies **are now in phase II trials.**

Kay Blennow, The Lancet, July 2006

CAD106 : struttura



Qβ-VLP

Produced in E.coli

Linker

(SMPH, commercially available)

Peptide:

Ab_{1-6} - Spacer

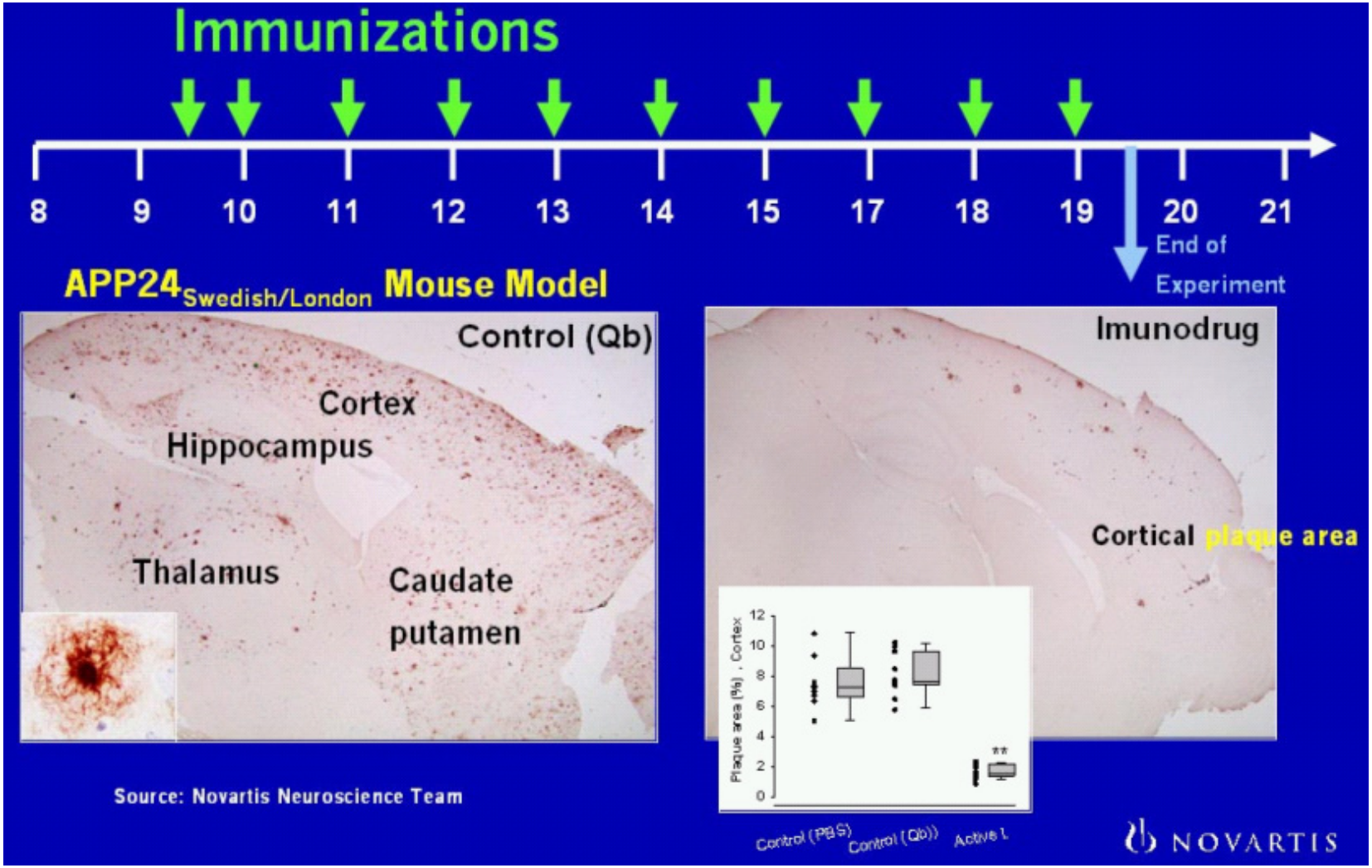
Produced by solid phase peptide synthesis

Qβ-VLP-Aβ1-6

CAD106

Drug Substance

CAD 106: inibizione deposizione β-amiloide



Sperimentazioni

- Aβ Fibrillisation inhibitors (Alzhemed-phase III)
- NGF therapy (phase I)
- Copper and zinc chelators (clioquinol, PBT-1) reduces Aβ deposition in transgenic mice (phase II trial, halted)
- Anti-tau drugs (reducing tau-phosphorylation by inhibiting tau kinases [CDK5, GSK-3 β] pre-clinical phase)

Drugs candidates based on epidemiology

Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies

- NSAIDs offer some protection against the development of AD, but the appropriate dosage and duration of drug use and the ratios of risk to benefit remains still unclear

Etminan M et al, BMJ, 2003

Estrogeni & AD

- Epidemiologic studies suggest that estrogen may be protective against the development of AD, and from this observation, the possibility that it also have a therapeutic effect in AD has been suggested. To date, two well designed clinical trials examining the ability of Premarin (R) to slow the rate of decline in women with AD were **negative**

Doody RS, Neurology 2001

Cholesterol-lowering drugs

- Il primo link fu dovuto all'osservazione che conigli con dieta ricca di colesterolo accumulavano Aβ intracellulare.
- Studi retrospettivi indicavano che l'uso di statine riduceva il rischio di sviluppare AD
- Studi su topi transgenici con AD hanno dimostrato che statine riducono accumulo di Aβ cerebrale.
- Studi prospettici di coorte tuttavia non hanno dimostrato l'associazione.
- Inoltre trials in pazienti con AD non hanno mostrato alcun cambiamento di Aβ nel plasma o nel CSF ed un RCT a 12 mesi con atorvastatina vs placebo ha mostrato solo un lievissimo miglioramento

Kay Blennow, The Lancet, July 2006

Cosa possiamo utilizzare?

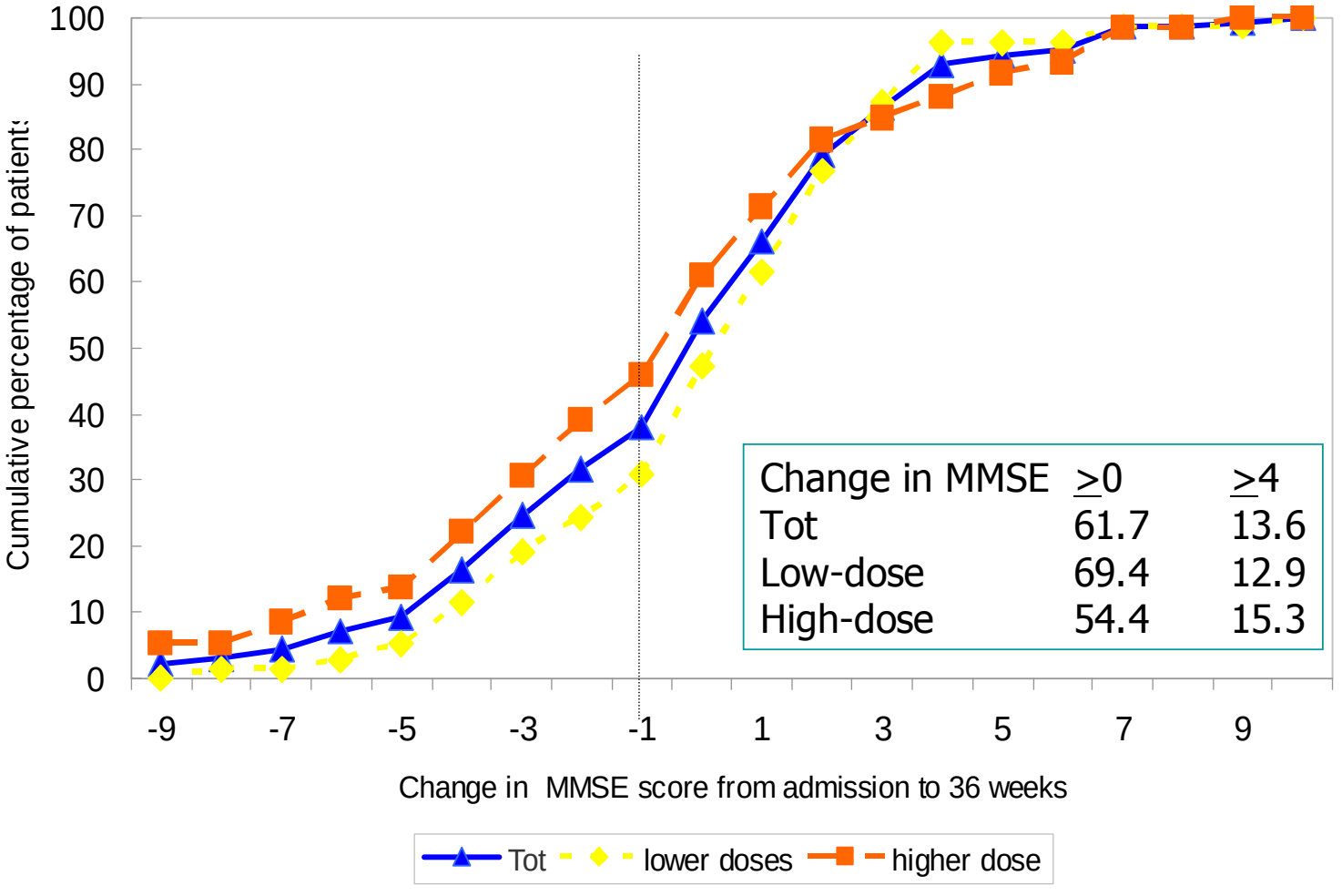
Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.*

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3–5	0.5–2	0.5–1	3–7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70–80	2†	5–7	60–80
Protein binding (%)	96	40	0–20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.
† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

Cummings; N Engl J Med 2004;351:56-67

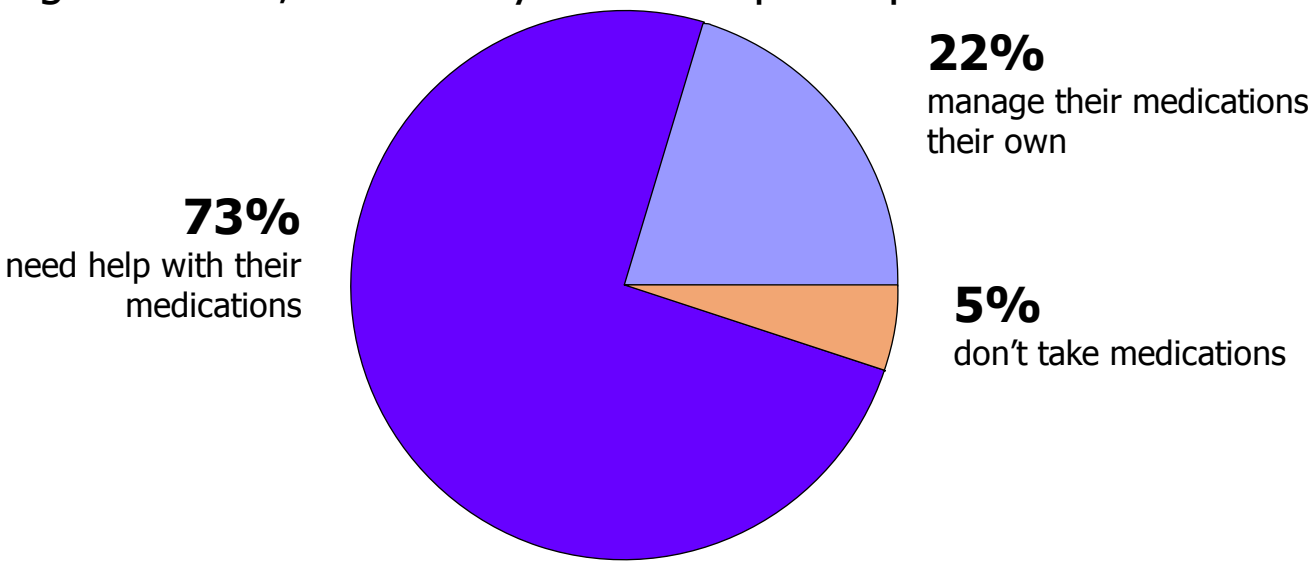
Cumulative distribution of patients with specified change from baseline in MMSE



Bellelli G et al, Aging Clin Exp Res 2006

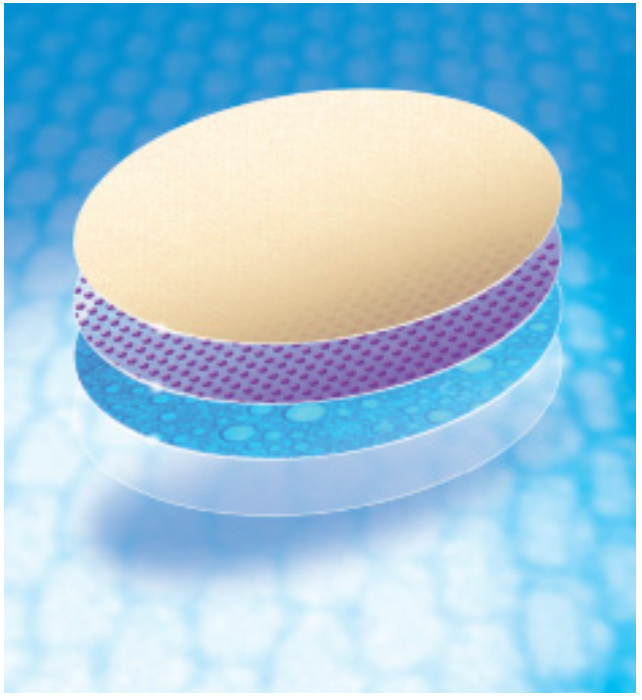
Managing Medications

- 73% of people with AD need help managing and taking their medications[1]
- Reduced drug burden or easier medication management can ease caregiver stress, which may in turn improve patient outcomes[2]



1. Alzheimer's Association and National Alliance for Caregiving, 2004 National Survey
2. Sink KM, et al. *J Am Geriatr Soc* 2006;54:796–803

Exelon® Patch Features Innovative New Generation Matrix Technology



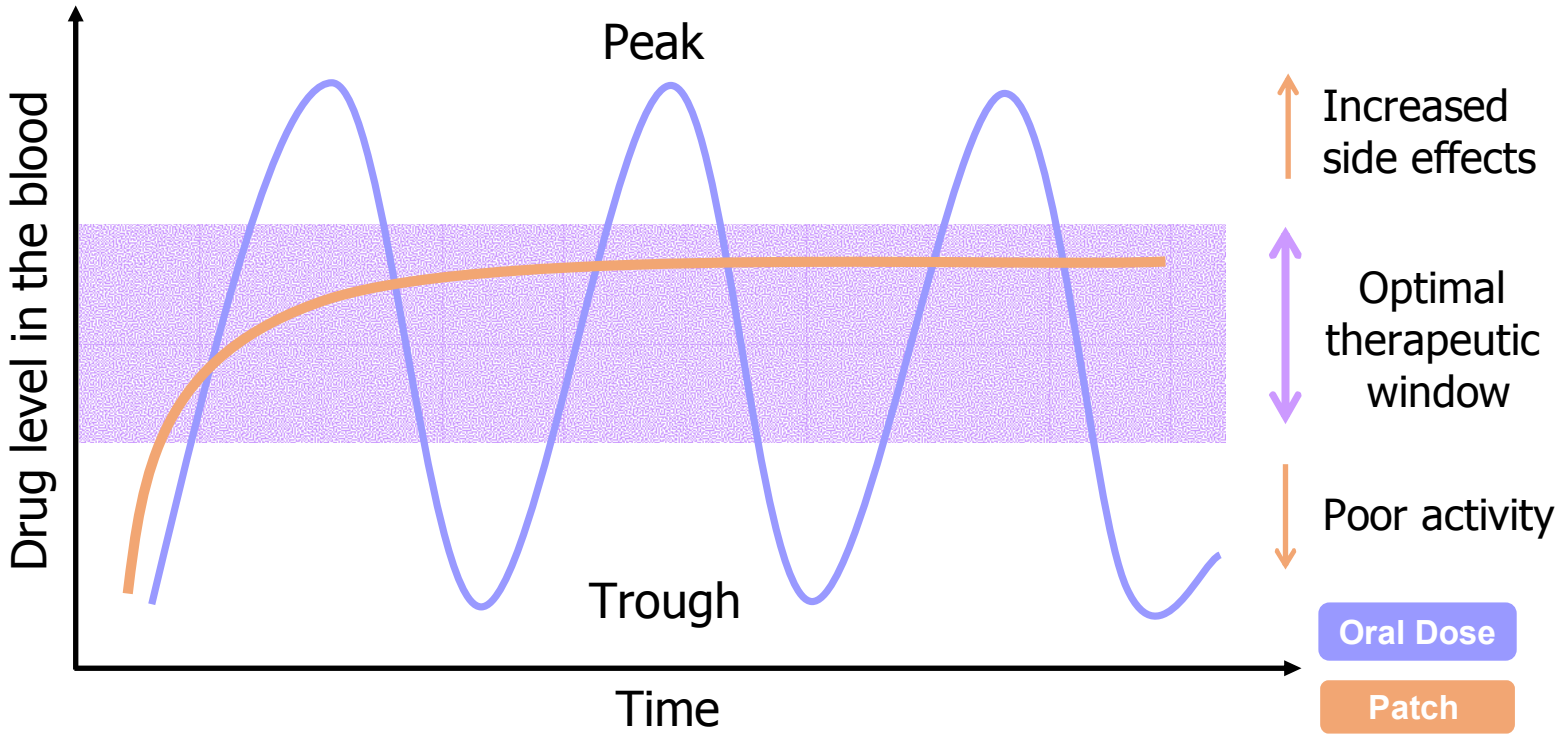
Coloured backing layer

Drug-containing matrix

Adhesive matrix

Release liner

Smooth, Continuous Delivery by Transdermal Patches Keeps Drug Levels in Optimal "*Therapeutic Window*"



Hypothetical presentation

Transdermal Patch for AD: Clinical benefits for the patients

- Improved pharmacokinetics
  - Smooth, continuous drug delivery
  - 24-hour coverage
- Avoids the gastrointestinal tract
  - Independent of food intake
- Avoids first-pass effect (not significantly metabolized by the hepatic P450 isoenzyme system)
- Fewer side effects

Investigation of transDermal Exelon in ALzheimer's disease (IDEAL)

- Multi-centre, randomized, double-blind, placebo- and active-controlled, parallel-group study
- 24-week duration
- 1,195 moderate Alzheimer's disease patients
- 100 study centres
- 21 countries (US, Latin America, Europe, Asia)

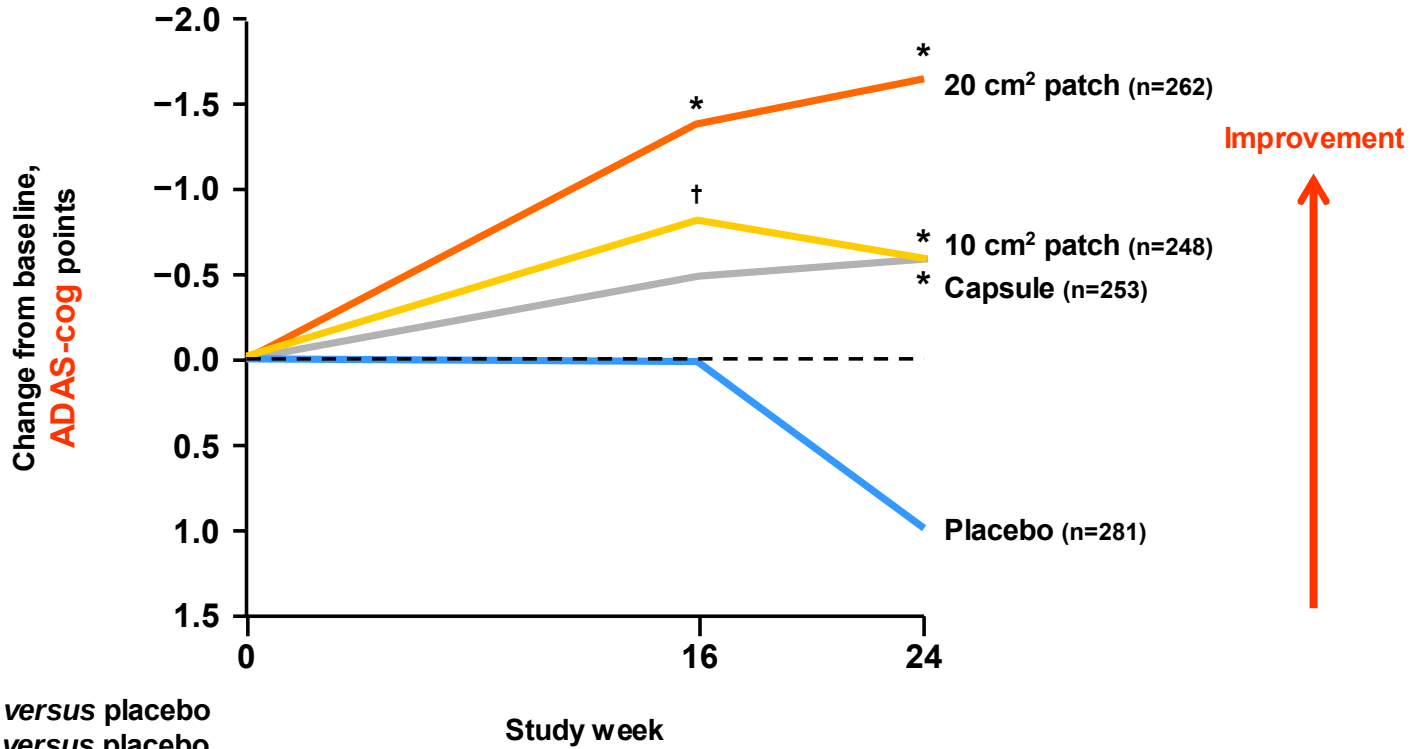
Patients: Inclusion Criteria

	Treatment group			
	Rivastigmine			Placebo ($n=302$)
	10 cm^2 patch ($n=291$)	20 cm^2 patch ($n=303$)	Capsules ($n=294$)	
Age, years				
Mean (SD)	73.6 (7.9)	74.2 (7.7)	72.8 (8.2)	73.9 (7.3)
Gender, %				
Male: Female	32.0: 68.0	34.0: 66.0	34.4: 65.6	33.4: 66.6
Ethnic origin, *n* (%)*				
Caucasian	220 (75.6)	227 (74.9)	219 (74.5)	227 (75.2)
Black	1 (0.3)	3 (1.0)	5 (1.7)	2 (0.7)
Oriental	25 (8.6)	27 (8.9)	29 (9.9)	27 (8.9)
Other	45 (15.5)	46 (15.2)	41 (13.9)	46 (15.2)
Years of formal education, years,				
Mean (SD)	9.9 (4.3)	9.9 (4.4)	9.9 (4.4)	9.9 (4.3)
Alzheimer's disease duration, years**				
Mean (SD)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)
Living situation, *n* (%)				
Alone	43 (14.8)	30 (9.9)	35 (11.9)	27 (8.9)
With caregiver	240 (82.5)	265 (87.5)	255 (86.7)	264 (87.4)
Assisted living	8 (2.7)	8 (2.6)	4 (1.4)	11 (3.6)
Baseline MMSE				
Mean (SD) scores	16.6 (3.1)	16.6 (2.9)	16.4 (3.1)	16.4 (3.0)

*Collected on the case report form using categories 'Caucasian', 'Black', 'Oriental', or 'Other'.
**Time since first diagnosis by a physician.

ADAS-cog: Patch Superior to Placebo

Functions:
- Orientation
- Memory
- Language
- Visuospatial
- Praxis



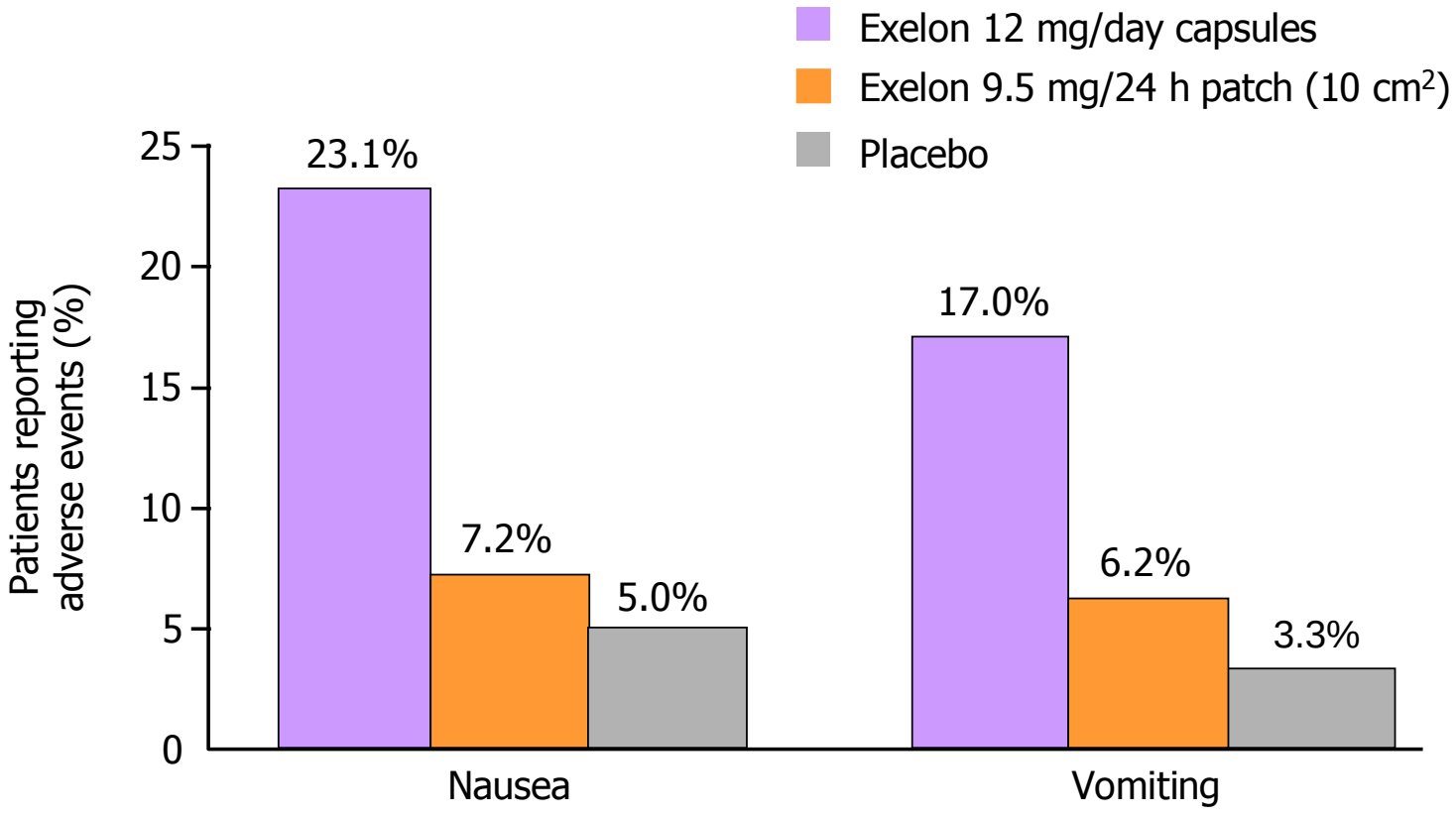
*$p < 0.05$ *versus* placebo
†$p = 0.09$ *versus* placebo
ITT-LOCF analysis

Winblad et al Int. J. Geriatr. Psychiatry

IDEAL 24-Week Efficacy Findings: Summary

- **10 cm^2 patch superior to placebo on measures of:**
  - **cognition (ADAS-cog and MMSE)**
  - **clinical global (ADCS-CGIC)**
  - **function (ADCS-ADL)**
  - **attention (TMT-A)**

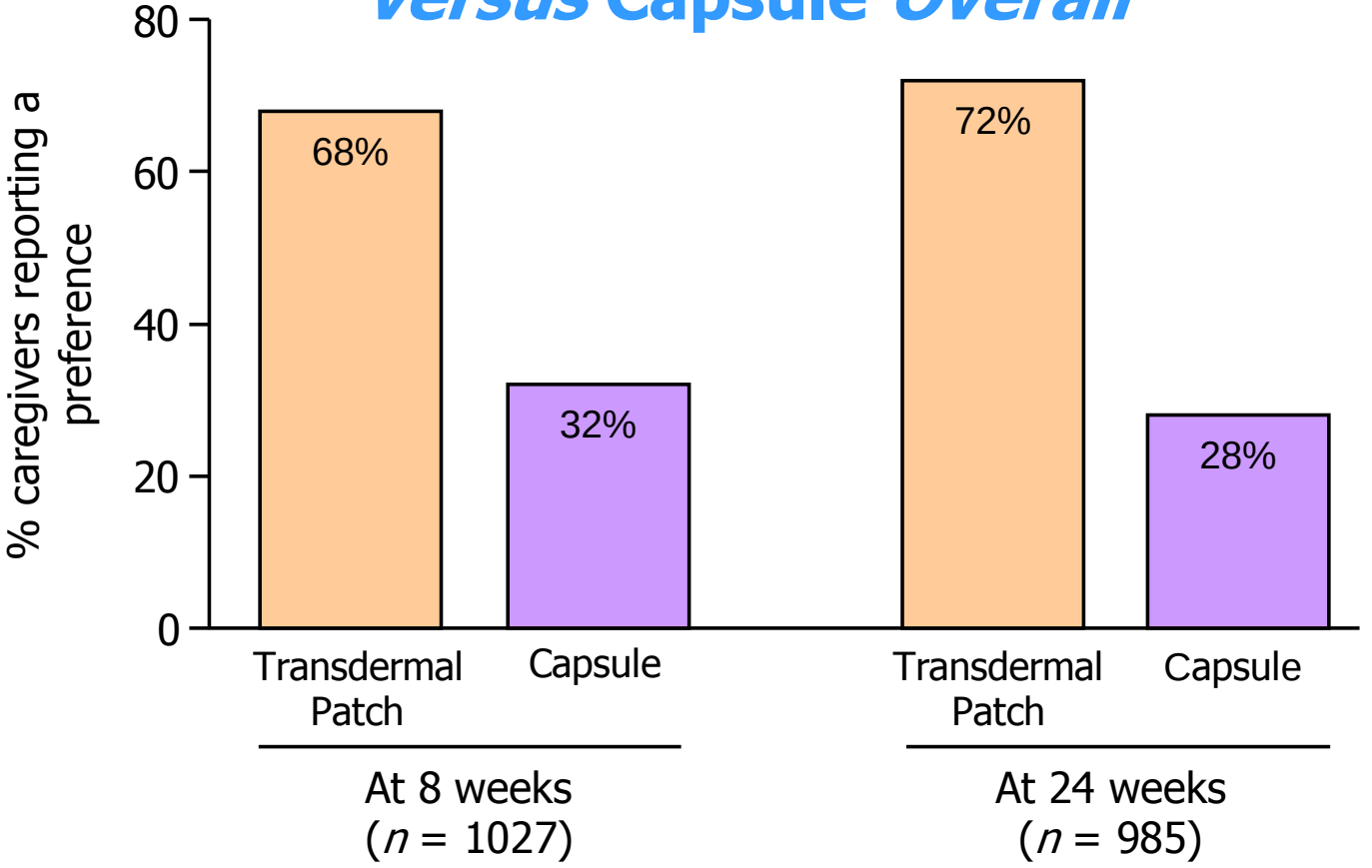
Three Times Fewer Reports of Nausea and Vomiting: Exelon® 9.5 mg/24 h Patch *versus* Capsules



Safety population

Winblad B, et al. *Int J Geriatr Psychiatry* 2007;22:456–67

Preference for Transdermal Patch *versus* Capsule *Overall*



Winblad B, et al. *Int J Geriatr Psychiatry* 2007;22:485–91

Blesa R, et al. *Neurology* 2007;69 (Suppl 1):S23–8

Conclusioni

- La scienza ha compiuto notevoli progressi nel campo della ricerca di terapie per la demenza
  - Sono in pipeline numerosi farmaci
  - γ e β secretasi (modulatori)
  - Immunizzazione
- Attualmente gli AChE-I sono i farmaci raccomandati nella demenza di Alzheimer
- La formulazione transdermica offre vantaggi in termini di modalità di rilascio del farmaco, compliance del paziente e preferenze del caregiver