Pharmacological Approaches for Cognition

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Conflict of Interest

	Name of Commercial Interest	Clinical Area/Topic
Grant/Research Support	Accera, Biogen, Eisai, Eli Lilly, Genentech, Roche, Lundbeck, Chase Pharmaceuticals	Alzheimer Disease
Speaker' s Bureau	Eisai, Pfizer, Forest, Novartis, Eli Lilly & Company	Alzheimer Disease
Consultant/Advisory Boards	Accera, Alltech, Avanir, Biogen, Eisai Med Res, Inc., FORUM Pharmaceuticals, Genentech, Inc., Grifols, Helicon, Inc Research, Lundbeck, Medavante, Medivation, Inc., Merck and Co. Inc., Neurotrope Biosciences, Novartis, Pfizer, Prana Biotech, QR Pharma, Roche, Sanofi-Aventis, Schering-Plough, Toyama Pharm., Lilly, UCB Pharma	Alzheimer Disease
	Elan	Transgenic mouse model patent that is licensed to Elan

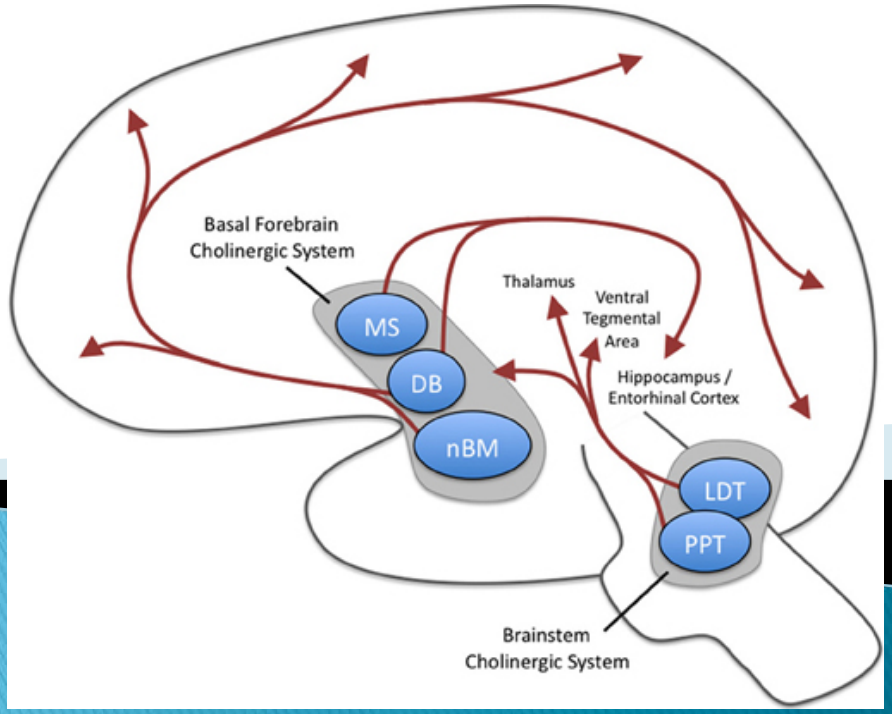
Agenda

I. Introduction – History of Cognitive Therapies for Dementia
II. Established Drugs for AD*
III. Evolution of Established Therapies
IV. Medical Foods
V. AD Drug Candidates with Efficacy Signals
VI. New Symptomatic Therapeutic Approaches in Development
VII. Future Directions for Cognitive Therapy in AD

Cholinergic Deficiency in Alzheimer's Disease

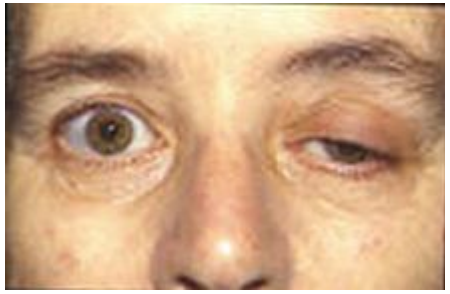
Peter Davies, Elaine Perry – Neuropathologic evidence for Cholinergic Deficit

Cholinergic Hypothesis

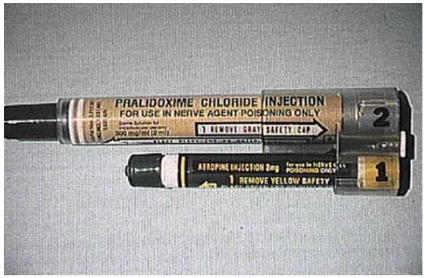


History of Cholinesterase Inhibitors

- Early use
- Myasthenia gravis –



- Posion gas (organaphosphates) –



- Pesticides – Sevin

Cholinesterase Inhibitors in AD

- First use in AD- series of experiments Leon Thal in the 80s with Physostigmine

- Use of oral THA in long-term treatment of senile dementia, Alzheimer's type. Summers WK, Majovski LJ, Marsh GM, Tachiki KH, Kling A. New England Journal of Medicine 1986; 315: 1241-1245.ers

Established Therapeutic Strategies for AD

Drug	Properties	Schedule	Starting Dose Titration	Maximum Dose
Donepezil	ACh specificity	5 mg QD	↑ to 10 mg at 6W	10 mg QD
Rivastigmine	BCh specificity	1.5 mg BID	↑ by 1.5 mg Q6W	6 mg BID
Galantamine	NR modulator	4 mg BID	↑ by 4 mg Q6W	12 mg BID
Memantine	NMDA-ra	5 mg BID	↑ by 5 mg QW	10 mg BID

ACh: acetylcholinesterase; BCh: butyrylcholinesterase; NMDA-RA: N-methyl-D-aspartate receptor antagonist; NR: nicotinic receptor; QW: every week; Q6W: every 6 weeks.

1. Birks J. *Cochrane Database Syst Rev*. 2006 25;(1):CD005593.
2. Emre M, Mecocci P, Stender K. *J Alzheimers Dis*. 2008;14:193-199.
3. Homma A et al. *Dement Geriatr Cogn Disord.* 2008;25:399-407.

Common Side Effects
Associated with Available Therapies for AD

Cholinesterase Inhibitors	Memantine
Nausea/vomiting	Confusion
Diarrhea	Sedation
Loss of appetite	Constipation
Dizziness	
Frank syncope	
Leg cramps	
Ulcers	
Cardiac arrhythmias	

Birks J. *Cochrane Database Syst Rev*. 2006 Jan 25;(1):CD005593. Emre M, Mecocci P, Stender K. *J Alzheimers Dis*. 2008;14:193-199. Homma A et al. *Dement Geriatr Cogn Disord*. 2008;25:399-407.

Evolution of First Generation of Drug Therapies for AD

- More convenient dosing
- Minimize adverse effects
- Extend utility across disease stages
- Derive approach to late treatment failures
- Broaden dementia indications for cognitive drug therapies

2nd Generation Cholinesterase Inhibitor and Memantine Therapy for Alzheimer's Disease

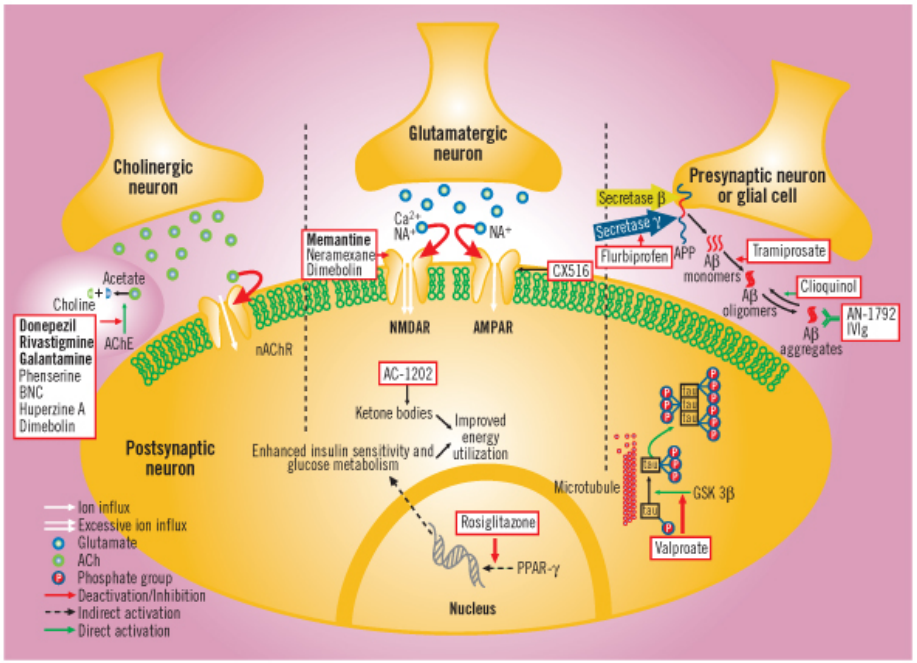
Improve Dosing Convenience

- Galantamine XL dosing (comparable efficacy to BID)
- Rivastigmine Patch (IDEAL Study)
  (2/3 reduction in GI adverse effects and comparable efficacy to BID capsules)
- Namenda XR comparable efficacy to BID dosing

Late Treatment Failure

- Dosage escalation
- Combination therapy

FIGURE 1
PROPOSED MOLECULAR MECHANISMS BEHIND THE CURRENT TREATMENT APPROACHES TO ALZHEIMER'S DISEASE*

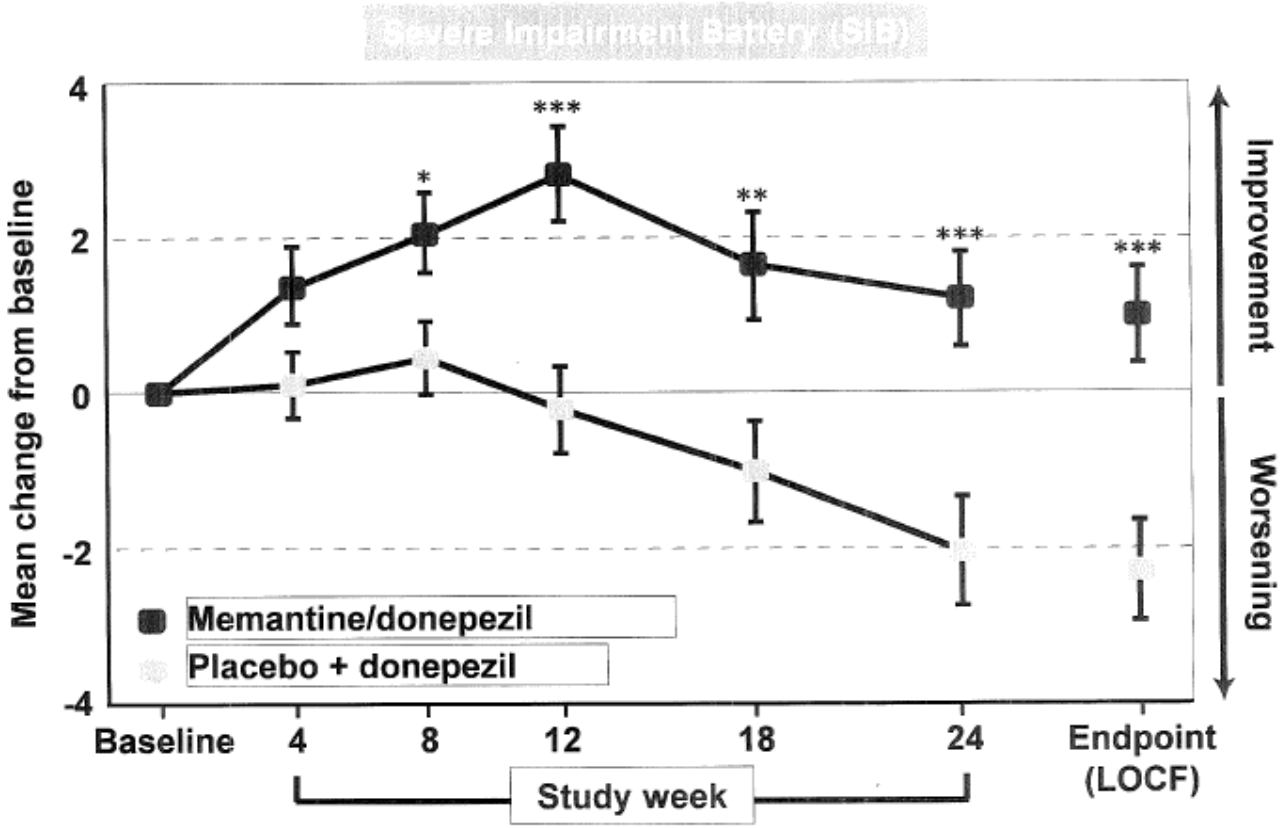


*Compounds that are currently being investigated as Alzheimer's disease therapeutic agents are boxed in red, with approved therapies indicated by bold letters. For more details about mechanisms, please refer to the text.

Ach=acetylcholine; AChE=acetylcholinesterase; Aβ=β-amyloid; AMPAR=α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; APP=amyloid precursor protein; GSK3=glycogen synthase kinase 3; nAChR=nicotinic acetylcholine receptor; NMDAR=*N*-methyl-D-aspartate receptor; PPAR-γ=peroxisome proliferation-activated receptor γ.

Grossberg GT, Pejovic V, Miller ML. *Primary Psychiatry.* Vol 14, No 8. 2007.

Donepezil/memantine combination in moderate-severe AD (MMSE 5-14):cognition



*p<0.05; **p<0.01; ***p<0.001 versus placebo + donepezil

Tariot et al. JAMA 2004; 291 (3): 317–324

Effectiveness and Tolerability of High-Dose (23 mg/d) Versus Standard-Dose (10 mg/d) Donepezil in Moderate to Severe Alzheimer's Disease: A 24-Week, Randomized, Double-Blind Study.

Clinical Therapeutics 32(7): 1234-1251, 2010.

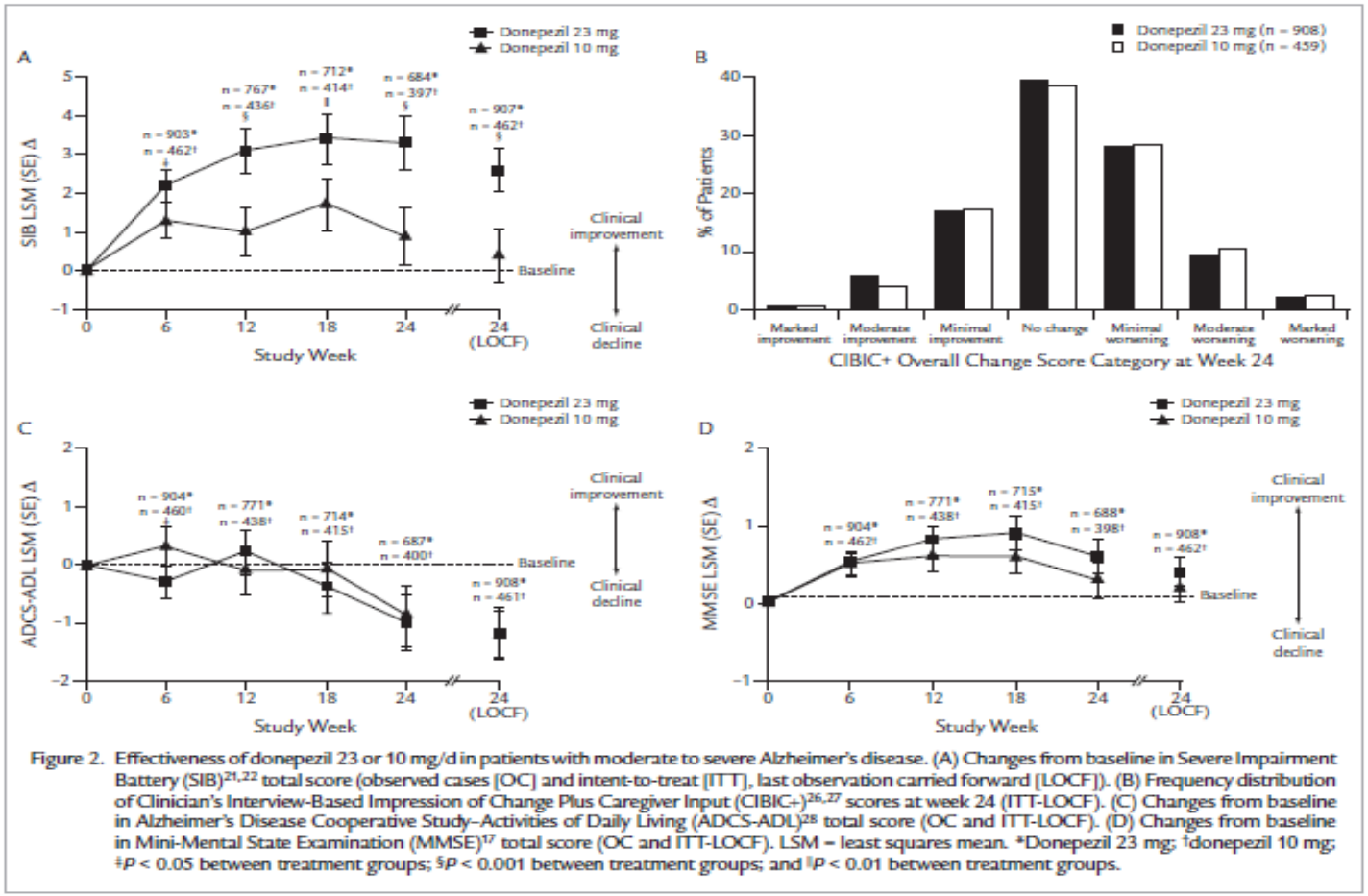
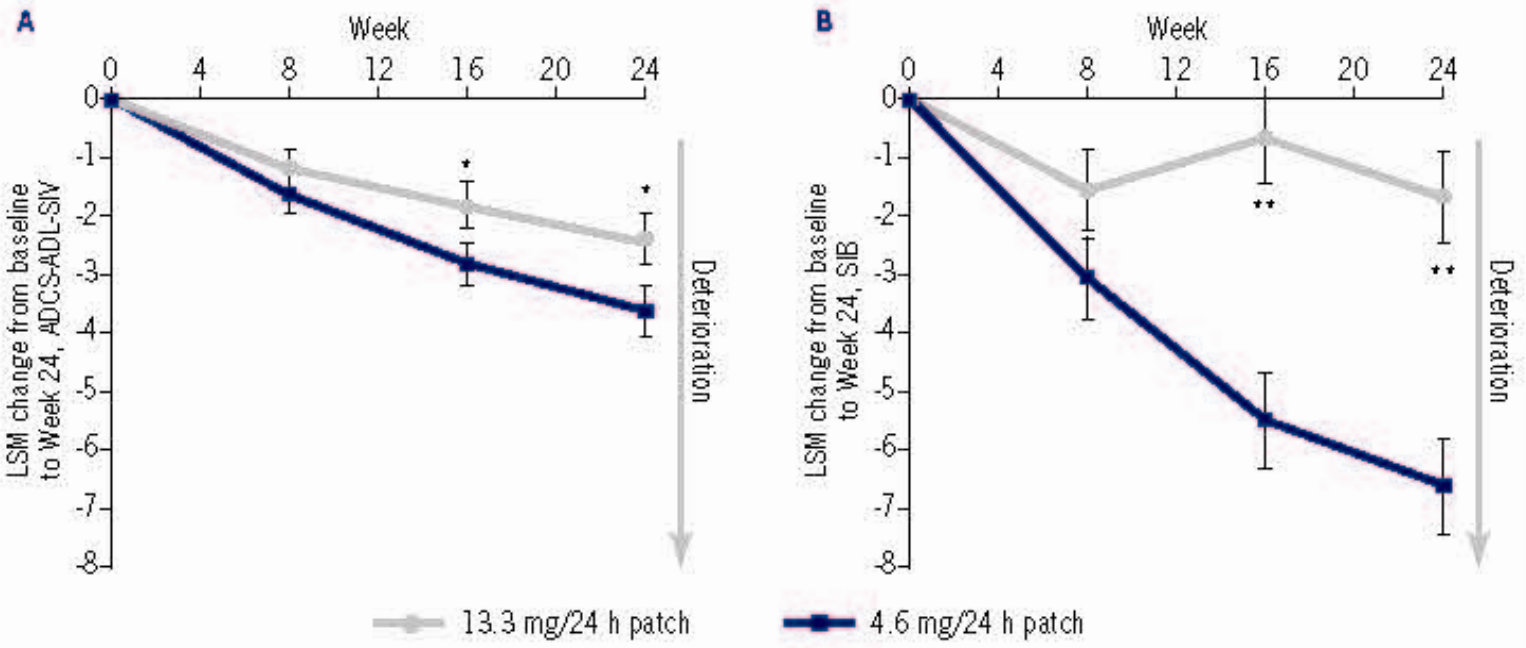


Figure 2. Effectiveness of donepezil 23 or 10 mg/d in patients with moderate to severe Alzheimer's disease. (A) Changes from baseline in Severe Impairment Battery (SIB)[21,22] total score (observed cases [OC] and intent-to-treat [ITT], last observation carried forward [LOCF]). (B) Frequency distribution of Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+)[26,27] scores at week 24 (ITT-LOCF). (C) Changes from baseline in Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)[28] total score (OC and ITT-LOCF). (D) Changes from baseline in Mini-Mental State Examination (MMSE)[17] total score (OC and ITT-LOCF). LSM = least squares mean. *Donepezil 23 mg; †donepezil 10 mg; ‡$P < 0.05$ between treatment groups; §$P < 0.001$ between treatment groups; and ‖$P < 0.01$ between treatment groups.

Efficacy, safety and tolerability of rivastigmine patch 13.3 mg/24h (15 cm^2) *versus* 4.6 mg/24h (5 cm^2) in patients with severe Alzheimer's disease: results of the ACTivities of daily living and cognitION (ACTION) study Martin R Farlow, Xiangyi Meng, Monique Somogyi

Figure 3: Change from baseline to Week 24 on (A) ADCS-ADL-SIV and (B) SIB score (Modified full analysis set).



ADCS-ADL-SIV, Alzheimer's Disease Cooperative Study–Activities of Daily Living scale–Severe Impairment Version; LSM, least square mean; SIB, Severe Impairment Battery. Modified full analysis set, population of patients including all randomized patients with at least one post-baseline efficacy measurement. Error bars represent the standard error of the LSM. The difference of LSM and p-values are obtained from an analysis of covariance model with treatment and pooled center as factors and baseline scores as a covariate. *$p < 0.05$ **$p < 0.0001$ *versus* 4.6 mg/24 h patch.

Metrifonate

- High dose AChE-I in mild-to-moderate AD – 90% cholinesterase inhibition
- 6 month – 2.75 point ADAS-cog point improved from baseline
- Downside – muscular weakness and respiratory failure

Broaden Spectrum of Dementia Diagnoses Benefits from Treatment

Rivastigmine for Dementia Associated with Parkinson's Disease

Murat Emre, M.D., Dag Aarsland, M.D., Ph.D., Alberto Albanese, M.D., E. Jane Byrne, F.R.C.Psych., M.B., Ch.B., Günther Deuschl, M.D., Peter P. De Deyn, M.D., Ph.D., Franck Durif, M.D., Ph.D., Jaime Kulisevsky, M.D., Ph.D., Teus van Laar, M.D., Ph.D., Andrew Lees, M.D., Werner Poewe, M.D., Alain Robillard, M.D., F.R.C.P.C., Mario M. Rosa, M.D., Erik Wolters, M.D., Ph.D., Peter Quarg, M.Sc., Sibel Tekin, M.D., and Roger Lane, M.D.

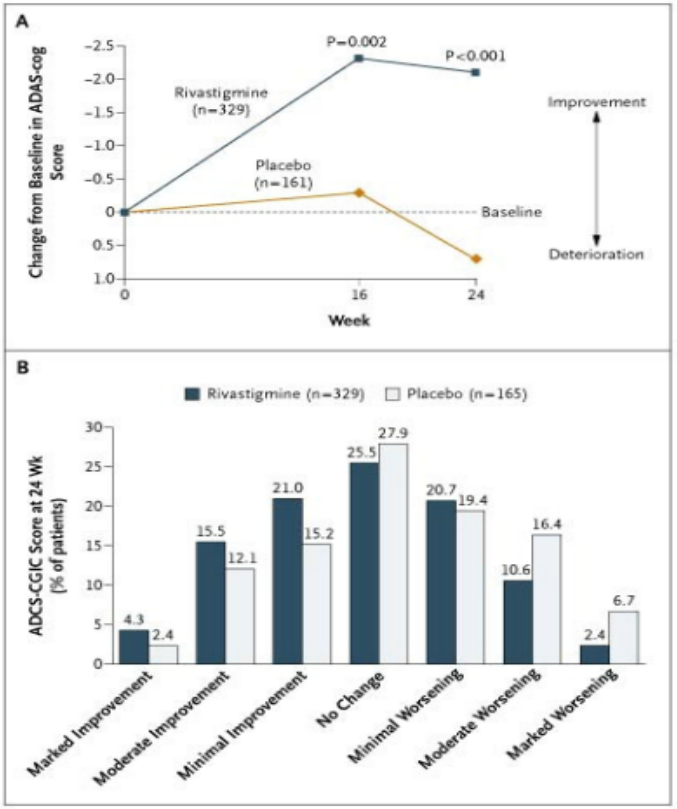
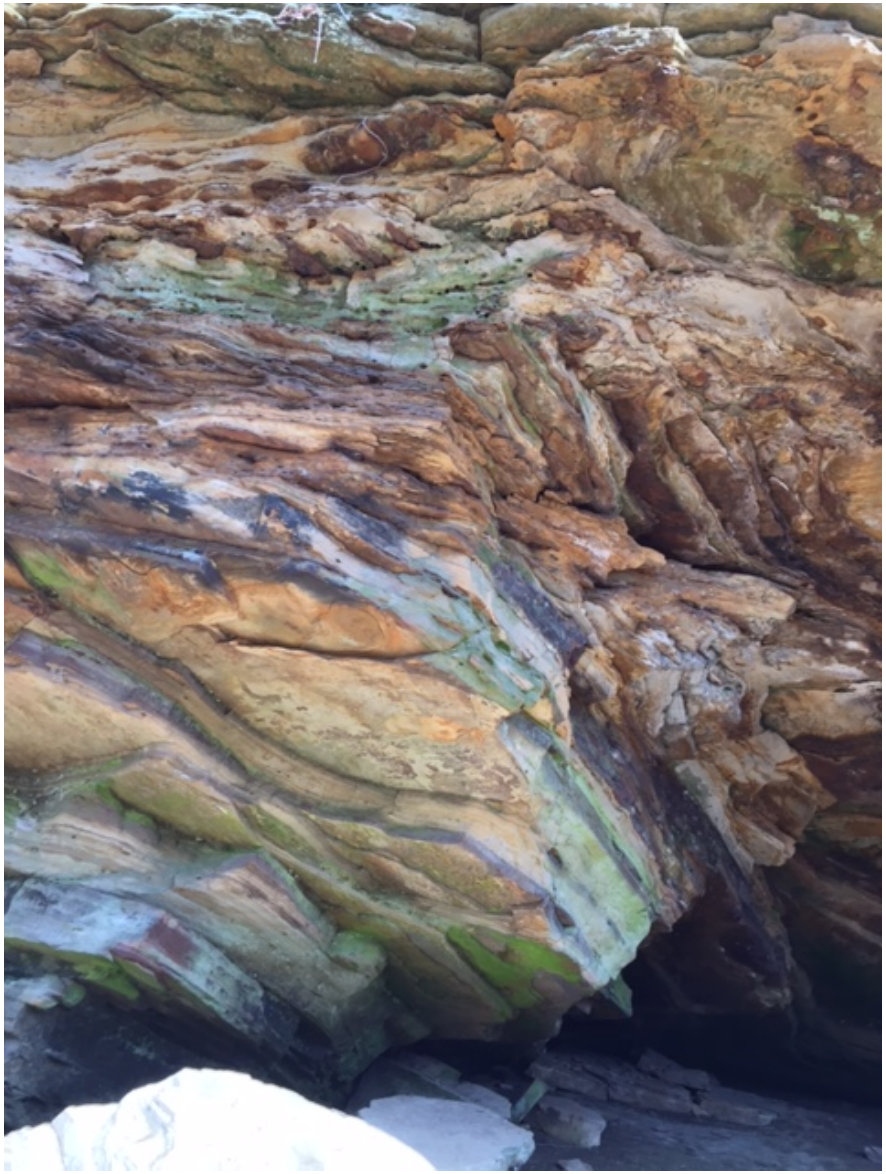


Figure 2. Results of the Primary Efficacy Analysis in the Efficacy Population.

Panel A shows the changes from baseline in the score for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). Scores can range from 0 to 70, with higher scores indicating more severe impairment and decreases in scores indicating improvement. Panel B shows the scores for the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC) at 24 weeks. Minimal changes were predefined as those that were clinically detectable but that did not affect a patient's clinical status; moderate changes were defined as definite, detectable changes that had a corresponding effect on clinical status; and marked changes were defined as those that had a dramatic effect on clinical status. P=0.007 for the overall difference between groups at 24 weeks. A few patients in the efficacy analysis had missing data on either of the two primary end points at week 24.



Amyloid imaging and memory change for prediction of cognitive impairment

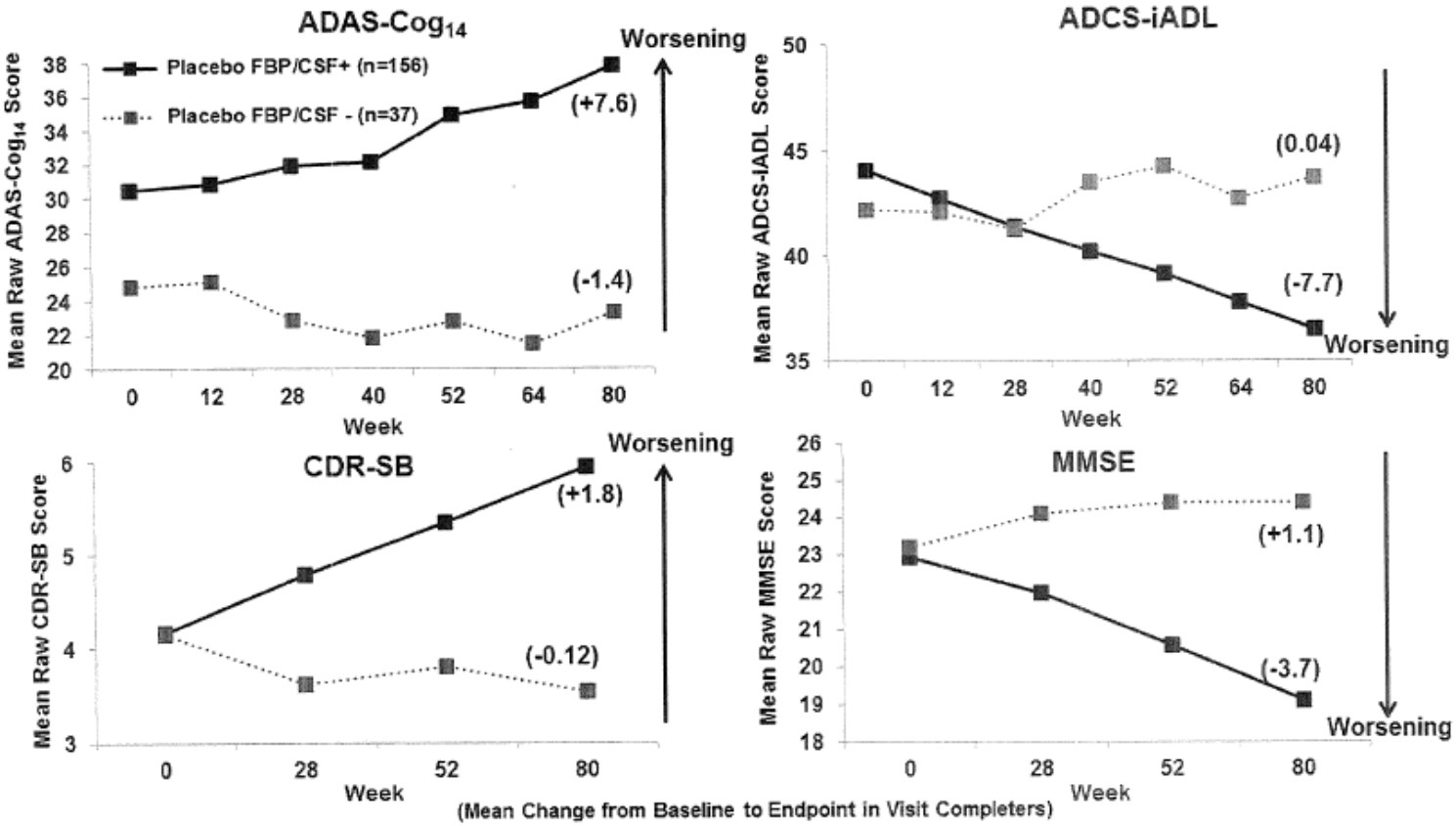
Table 3. Amyloid imaging and prediction of conversion to Alzheimer's disease

Study	Year	Radiotracer	Sample[a]	Number of subjects[a]	Mean age (SD)	Method	Findings
Okello *et al.* [24]	2009	PiB	MCI	31	69.4 (7.9)	SUVR	82% PiB-positive MCI convert to AD compared to 7% of PiB-negative MCI 47% PiB-positive MCI who convert to AD within 1 year have higher PiB in anterior cingulate and frontal cortex ($P < 0.05$), APOE ε4 is associated with faster conversion rates in PiB-positive MCI ($P < 0.05$)
Wolk *et al.* [25]	2009	PiB	MCI	26 (23 with follow-up)	70.2 (8.8)	DVR	38% PiB-positive MCI but no PiB- convert to AD over 22 months
Morris *et al.* [45]	2009	PiB	CN	159	71.5 (8.6)	BP	Higher PiB retention predicts progression from CDR 0 to MCI (hazard ratio = 2.74) and AD (hazard ratio = 4.85) over mean 2.4 years
Koivunen *et al.* [44]	2008	PiB	aMCI	15	71.1 (7.2)	SUVR, DVR	Elevated PiB in six converters in posterior cingulate and frontal cortex as well as elevated neocortical score
Forsberg *et al.* [23]	2008	PiB	MCI	21	63.3 (7.8)	SUVR	Higher PiB retention in frontal, parietal, and temporal cortices ($P < 0.01$) in MCI converters than CN individuals Higher PiB retention in posterior cingulate gyrus in MCI converters than MCI nonconverters ($P < 0.01$) No difference in PiB retention between MCI converters and AD
Small *et al.* [20]	2006	[^{18}F]FDDNP	AD, MCI, CN	4 MCI, 8 CN	NA for this subset	DVR	Three disease progressors had increases in [^{18}F]FDDNP between 5.5% to 11.2% compared to ≤3% in nine non-progressors

[a]In some cases a study subsample. AD, Alzheimer's disease; aMCI, amnestic MCI; APOE, Apolipoprotein E; BP, binding potential; CN, cognitively normal; DVR, distribution volume ratio; MCI, mild cognitive impairment; NA, not available; PiB, [^{11}C]Pittsburgh Compound-B; SD, standard deviation; SUVR, standard uptake value ratio.

Resnick et al Alzheimer's Research & Therapy 2011, 3:3

Clinical Progression in EXPEDITION1 and EXPEDITION2 Placebo-Treated Mild AD Patients Based on Evidence of Amyloid Pathology by Florbetapir ^{18}F or CSF $A\beta_{1-42}$



Dean R, Shaw L, et al. Inclusion of Patients with Alzheimer's Disease Pathology in Solanezumab EXPEDITION3 using Florbetapir (18F) PET Imaging or INNO-BIA AlzBio3 CSF Aβ1-42. Poster Presented at The Alzheimer's Association International Conference (AAIC); 2014 July 12-17; Copenhagen, Denmark

Implications of Amyloid Plaque Positive vs Negative Dementia

- Previous long-term open-label phase for ChE-I trials likely reflect selection bias for continuing drug to patients who are amyloid negative and non-progressors
- Previous MCI delay to conversion studies suggesting ApoE4 patients benefit from ChE-I therapy. May be amyloid positive patients derive greatest symptomatic benefits

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- Need Cholinesterase Inhibitor and possibly memantine trial in patients who meet clinical criteria for AD but are negative for amyloid

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

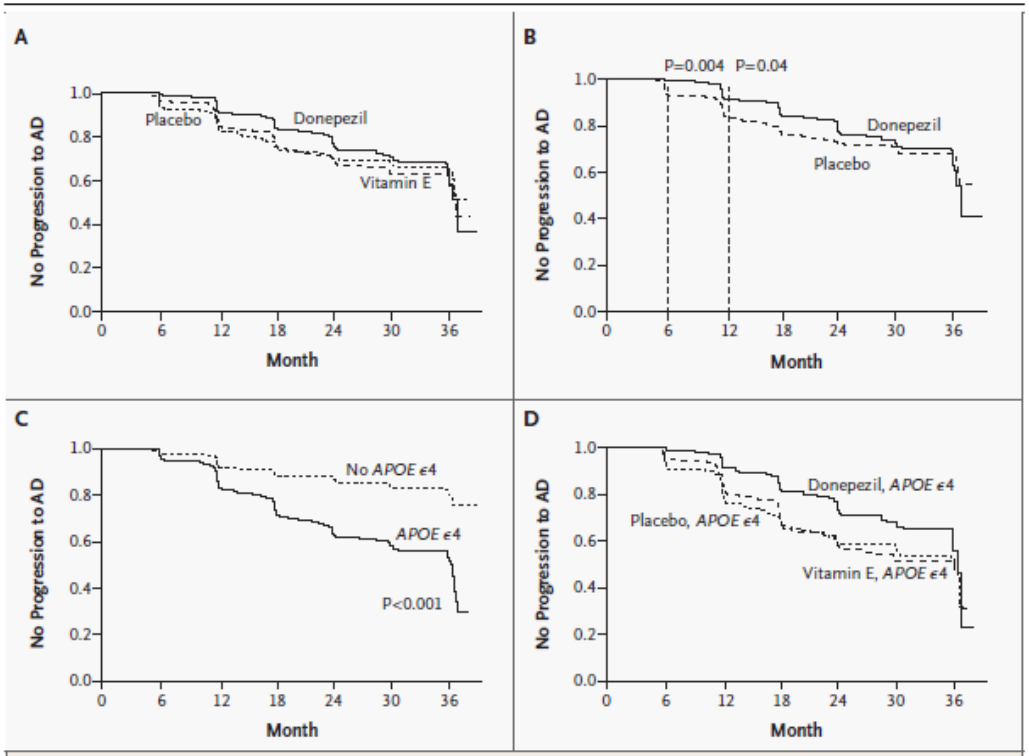
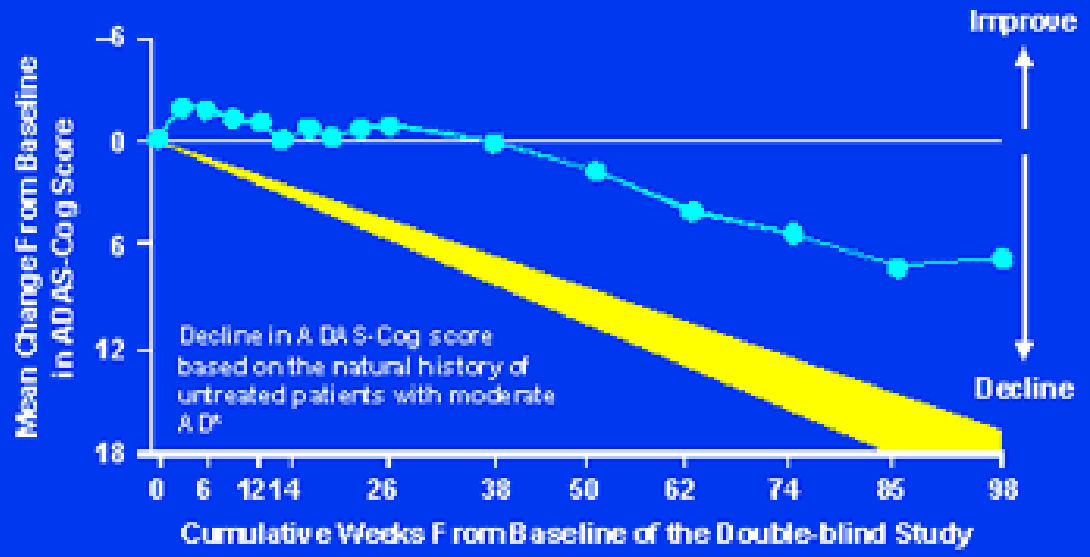


Figure 1. Kaplan–Meier Estimates of the Rate of Progression from Mild Cognitive Impairment to Alzheimer's Disease (AD).
Panel A shows the survival estimates in all three groups during the three-year study. Panel B shows the results of prespecified comparisons involving z-tests at 6 months (P=0.004) and 12 months (P=0.04). Panel C shows the effect of *APOE* ϵ4 carrier status on the rate of progression to Alzheimer's disease, and Panel D shows the effect of treatment among *APOE* ϵ4 carriers. Comparisons were adjusted for multiple comparisons with the use of the Hochberg method.

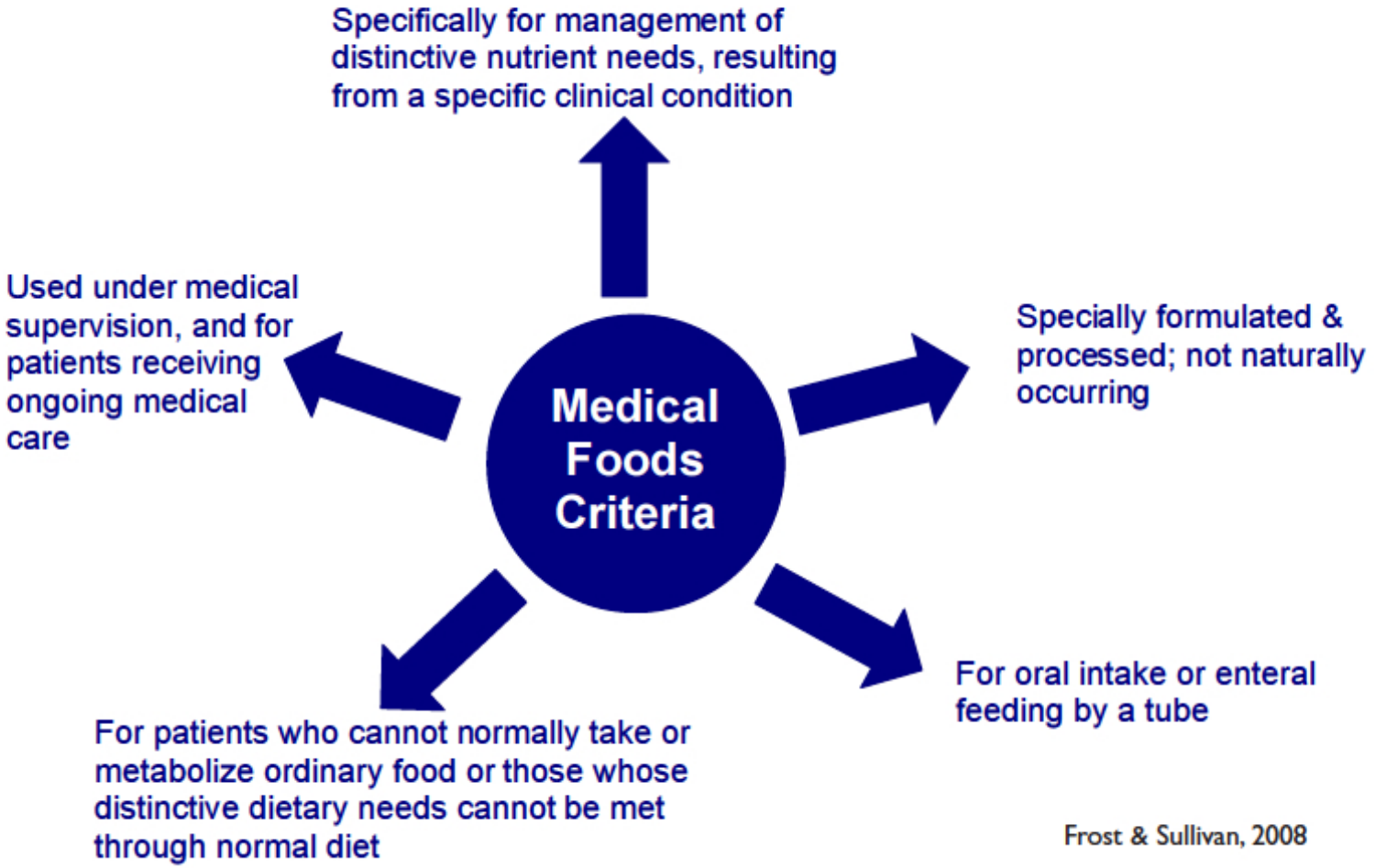
Medscape® www.medscape.com

Long-term Effects of Donepezil on Cognition: ADAS-Cog Mean Change From Baseline



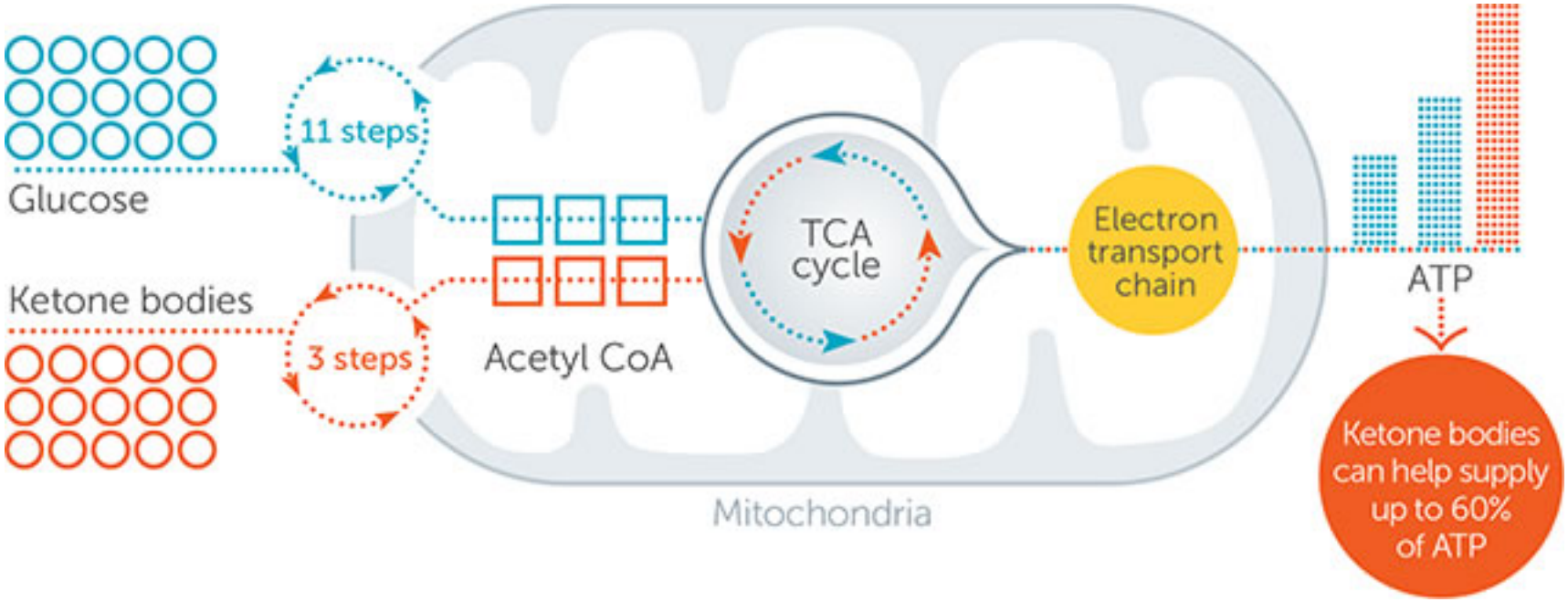
Medical Foods

Figure 1: Criteria for Medical Foods, Nutrition Labeling and Education Act of 1990

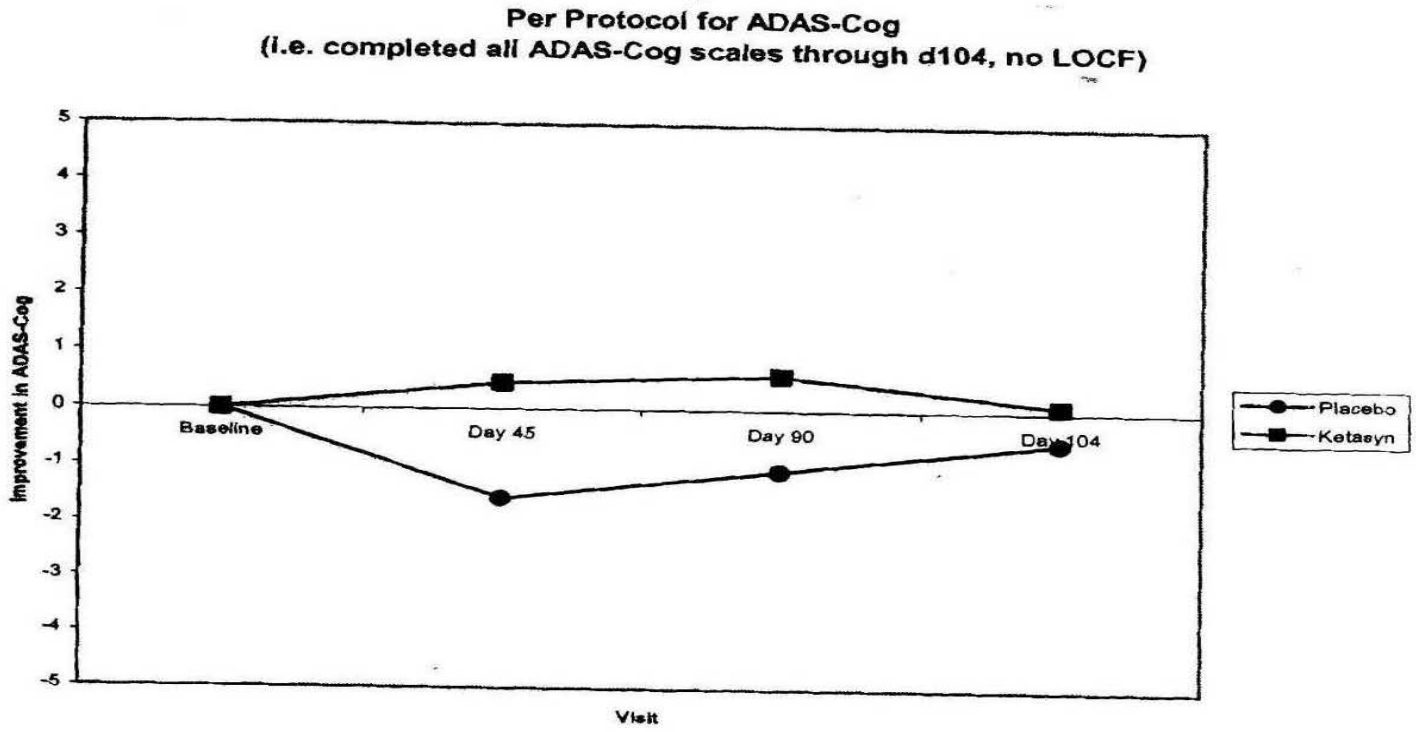


Frost & Sullivan, 2008

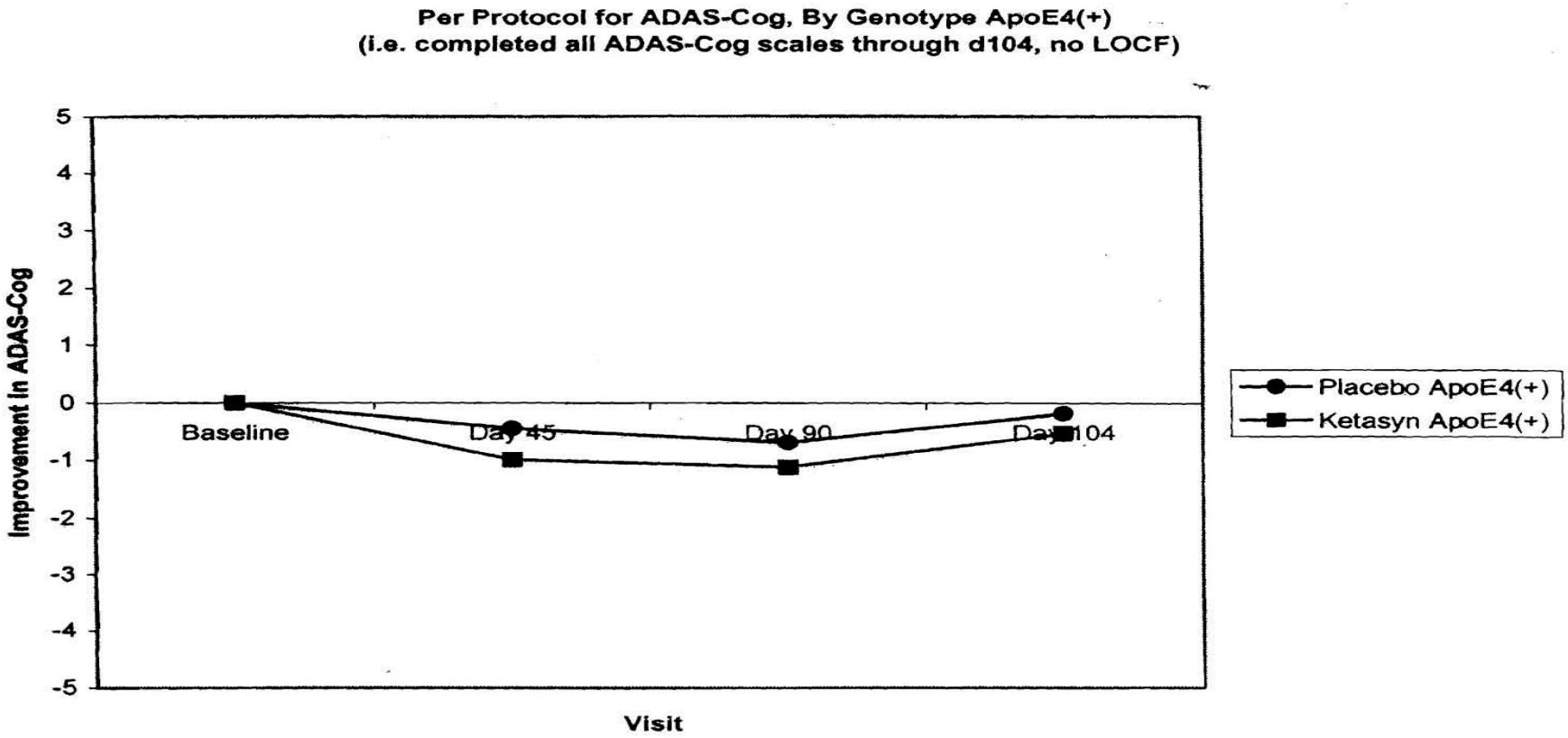
Axona/ketosyn mechanism



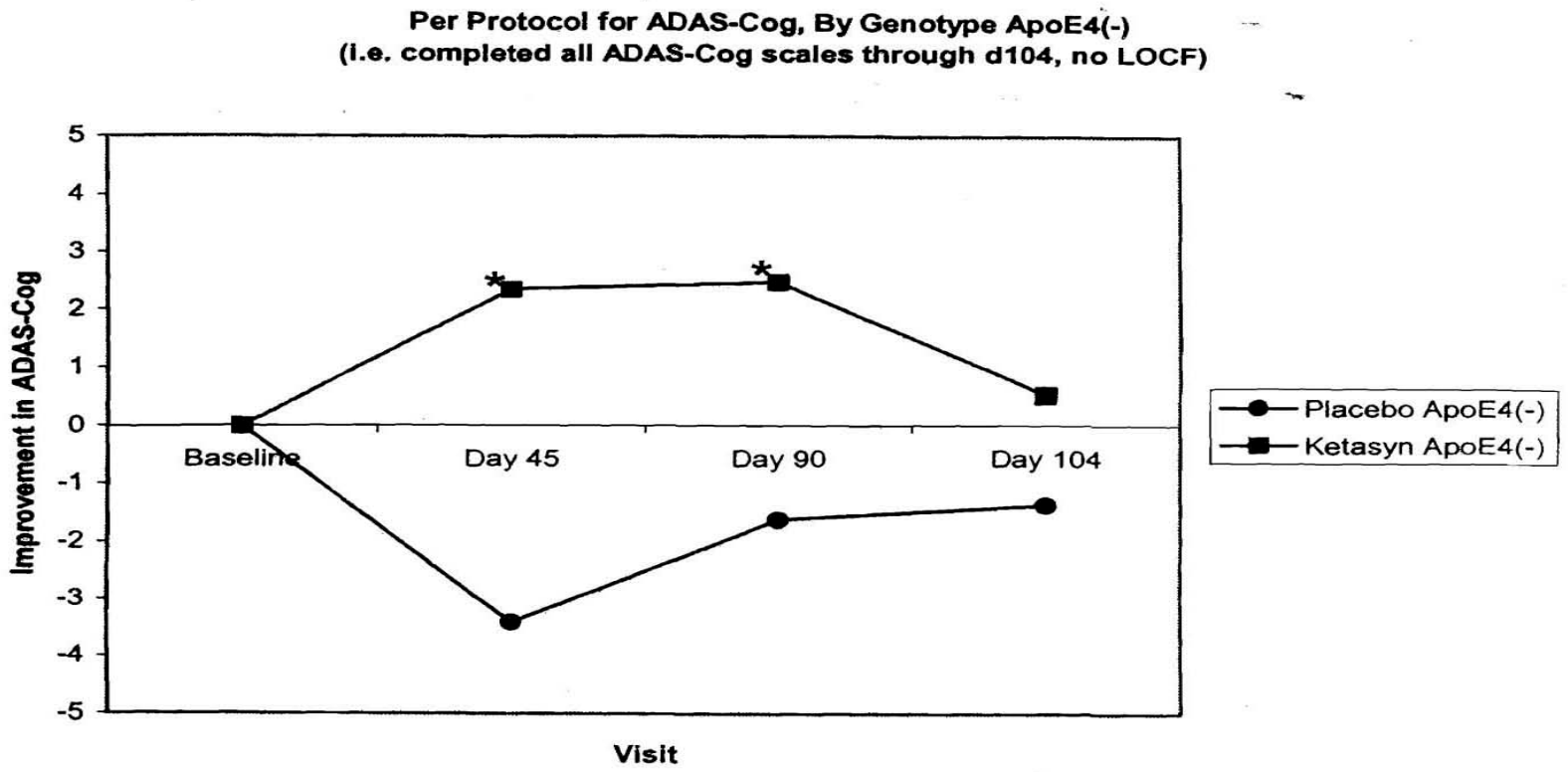
Ketosyn Phase II Trial



ADAS-Cog, by Genotype APOE4(+)

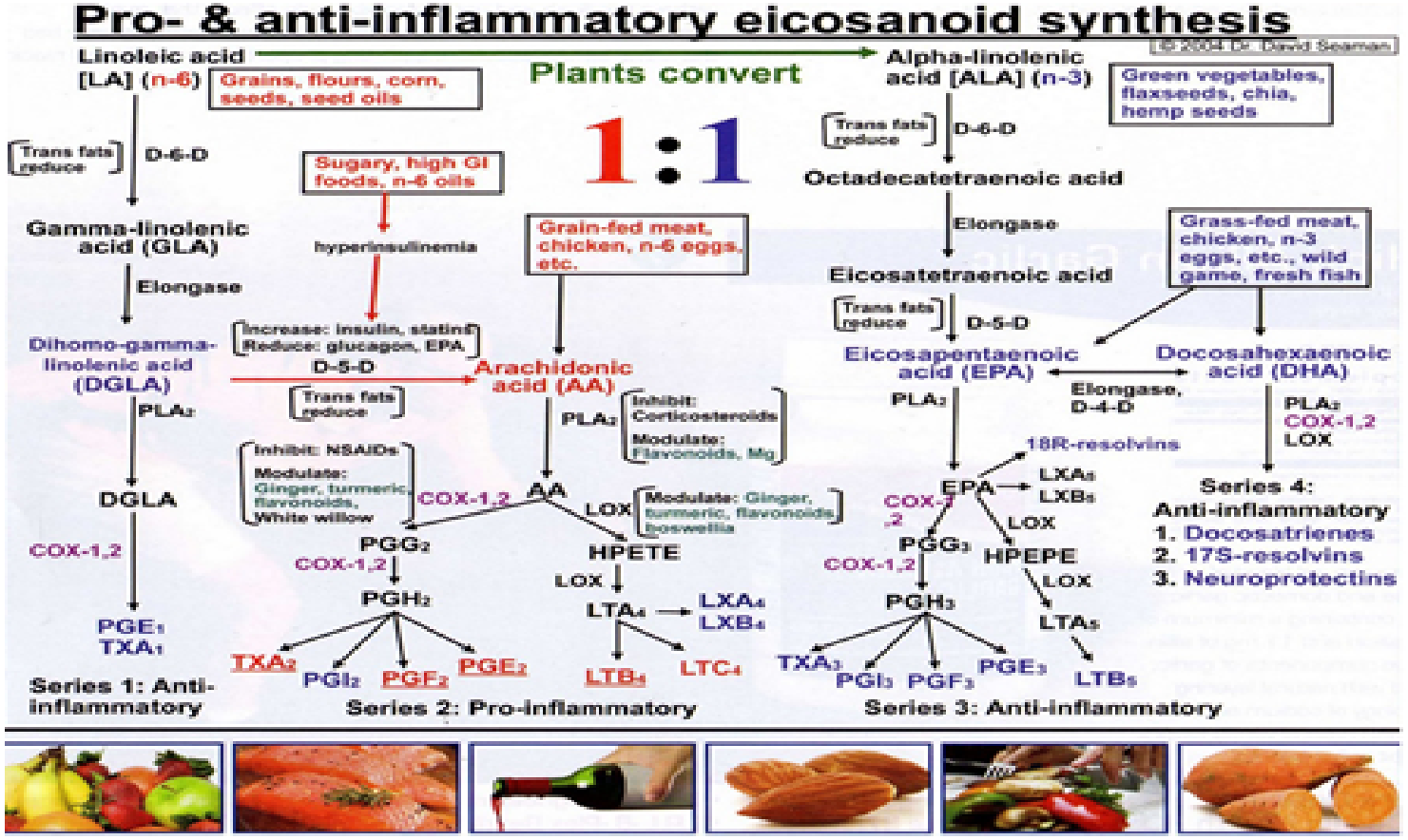


ADAS-Cog , by Genotype APOE4(-)

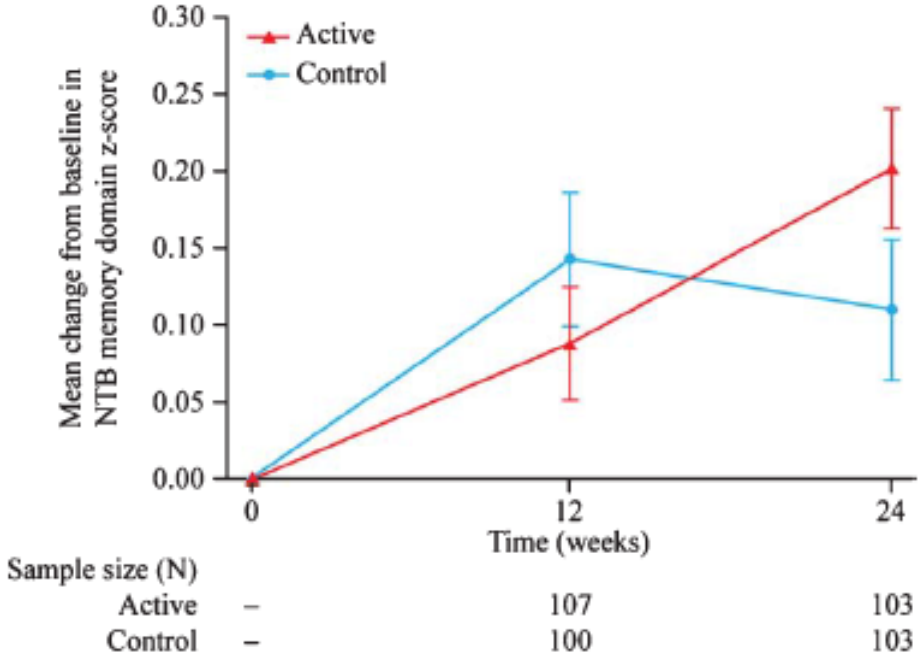


*FDA approved as Medial Food

Souvenaid


Pro- & anti-inflammatory eicosanoid synthesis
© 2004 Dr. David Seaman
Linoleic acid [LA] (n-6)
Grains, flours, corn, seeds, seed oils
Plants convert
1:1
Alpha-linolenic acid [ALA] (n-3)
Green vegetables, flaxseeds, chia, hemp seeds
Trans fats reduce
D-6-D
Gamma-linolenic acid (GLA)
Elongase
Dihomo-gamma-linolenic acid (DGLA)
PLA2
DGLA
COX-1,2
PGE1
TXA1
Series 1: Anti-inflammatory
Sugary, high GI foods, n-6 oils
hyperinsulinemia
Increase: insulin, statins
Reduce: glucagon, EPA
D-5-D
Trans fats reduce
Grain-fed meat, chicken, n-6 eggs, etc.
Arachidonic acid (AA)
Inhibit: Corticosteroids
Modulate: Flavonoids, Mg
Inhibit: NSAIDs
Modulate: Ginger, turmeric, flavonoids, White willow
COX-1,2
AA
LOX
Modulate: Ginger, turmeric, flavonoids, boswellia
PGG2
HPETE
PGH2
LTA4
LXA4
LXB4
TXA2
PGI2
PGF2
PGE2
LTB4
LTC4
Series 2: Pro-inflammatory
Octadecatetraenoic acid
Elongase
Eicosatetraenoic acid
Grass-fed meat, chicken, n-3 eggs, etc., wild game, fresh fish
Eicosapentaenoic acid (EPA)
Docosahexaenoic acid (DHA)
Elongase, D-4-D
PLA2
COX-1,2
LOX
18R-resolvins
EPA
LXA5
LXB5
PGG3
HPEPE
PGH3
LTA5
TXA3
PGI3
PGF3
PGE3
LTB5
Series 3: Anti-inflammatory
Series 4: Anti-inflammatory
1. Docosatrienes
2. 17S-resolvins
3. Neuroprotectins

Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized Controlled Trial



Scheltens, et. al, Journal of Alzheimer's Disease 31 (2012) 225–236

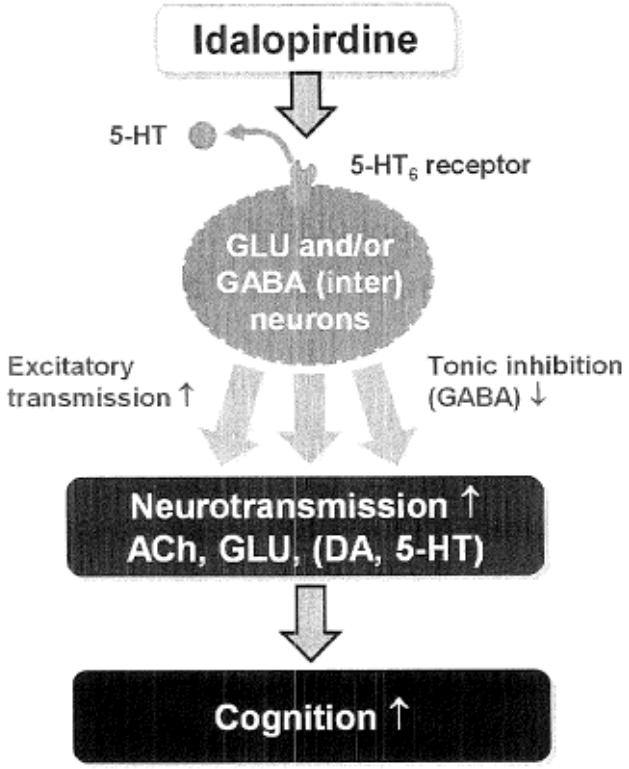
Drug Classes with Evidence for Efficacy but Failed in Development

- Muscarinic Agonists
- Ca+ Channel Blockers
- Nicotinic Agonists

New Directions in Sympomatic Drug Development

- Different less well studied mechanisms of action, different neurotransmitter systems
- Che-I/peripheral delivery blockade

Proposed MoA of idalopirdine



5-HT=serotonin; GABA=gamma aminobutyric acid; ACh=acetylcholine; DA=dopamine; MoA=mode of action

In cognition-relevant brain regions:

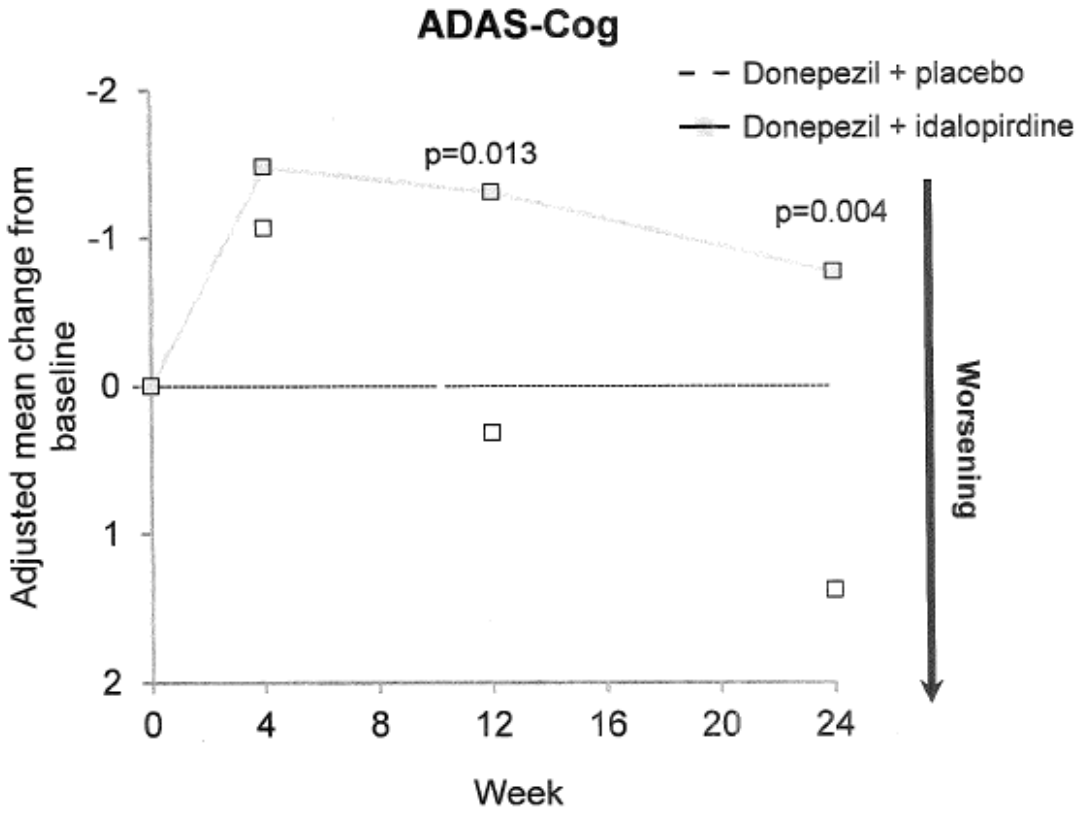
- **Impact on multiple neurotransmitters**
  - Facilitation of cholinergic, glutamatergic and, likely, monoaminergic signalling
- **Facilitation of neuronal activity**

Receptor localization and microdialysis data suggest regulation through:

- Glutamatergic pyramidal cells
- GABAergic (inter)neurons (reduced inhibition)

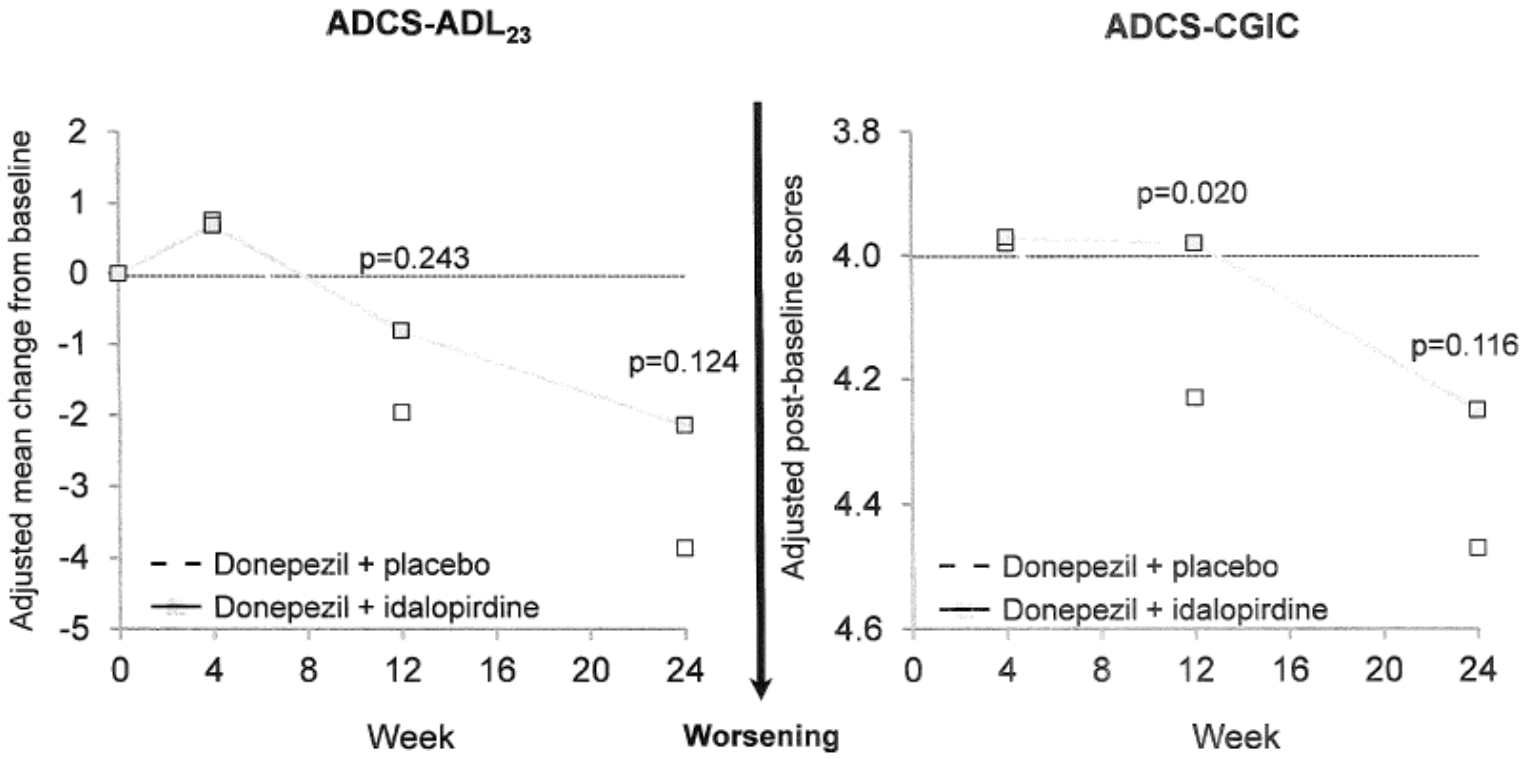
Added benefit in combination with cholinesterase inhibitors

Primary endpoint – cognition



Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099

Secondary endpoints – functional and global outcomes



Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099

Chase Pharma – AD Therapeutics

- Cholinesterase inhibitor dose in practice limited by adverse effects
- Only 20 to 30% inhibition of cholinesterase in the brain with high dose AChE-I in current use
- Decrease adverse effects, increase maximum tolerated dose by combining AChEI with peripheral cholinergic drug such as solifenacin
- Potential to increase dosing to 40 mg or more of donepezil, comparable increase with other cholinesterase inhibitor

Summary

- Slow evolutionary progression improving current medications
- Maximizing therapeutic benefit, more convenient dosing, minimizing adverse effects
- Expanding usage to broaden range of disease stage
- Expanding use to other dementias

Future Directions

Future

- Need for better targeting for symptomatic drugs regarding disease stage and diagnosis
- Continue evolving available cognitive therapies
- Investigate new potential disease mechanisms that may reveal symptomatic treatment targets

The End