

A Pragmatic Approach to the Clinical Treatment of Dementia

Byron Bair, M.D.

Associate Director GRECC, SLC VAMC

Professor of Internal Medicine & Psychiatry

University of Utah School of Medicine

AD Dementia Overview

- Demographics
- Pathophysiology
- Cognition & Symptoms
- Diagnosis
- Treatments
- Clinical strategy

Prevalence of Alzheimer's Disease

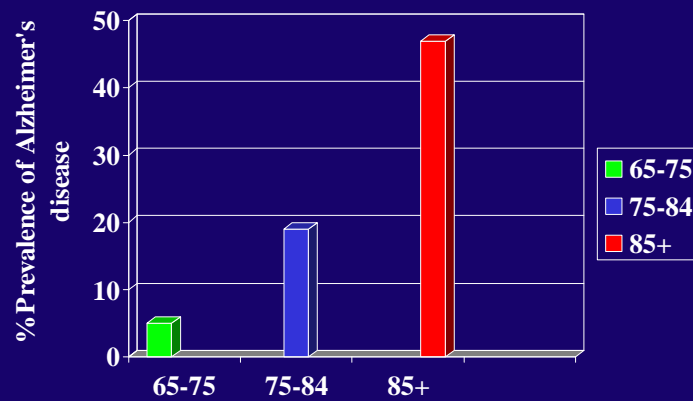
- Approximately 4 million Americans¹
- An estimated 50% of nursing home patients^{1,2}

¹Skelton VP III, Skelton NK. *Postgrad Med.* 1991;90:38-41.

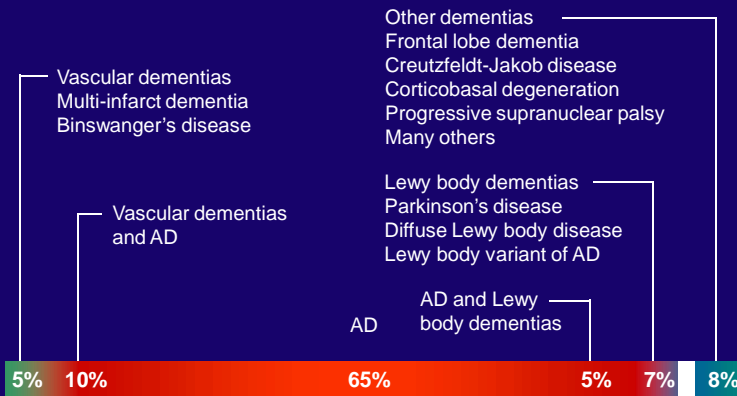
²Weiler PG. *Am J Public Health.* 1987;77:1157-1158.

Dementia & Age

Age Group (years)



Different Types Of Dementia



Small GW et al. *JAMA*. 1997;278:1363-1371.
 American Psychiatric Association. *Am J Psychiatry*. 1997;154(suppl):1-39.
 Morris JC. *Clin Geriatr Med*. 1994;10:257-276.

Bio Defects of Alzheimer's

Neuritic Plaques

B-amyloid peptides & APOE4

Beta amyloid precursor protein (APP)

beta amyloid peptides: Abeta 42 (diffuse); Abeta 40 (neuritic)

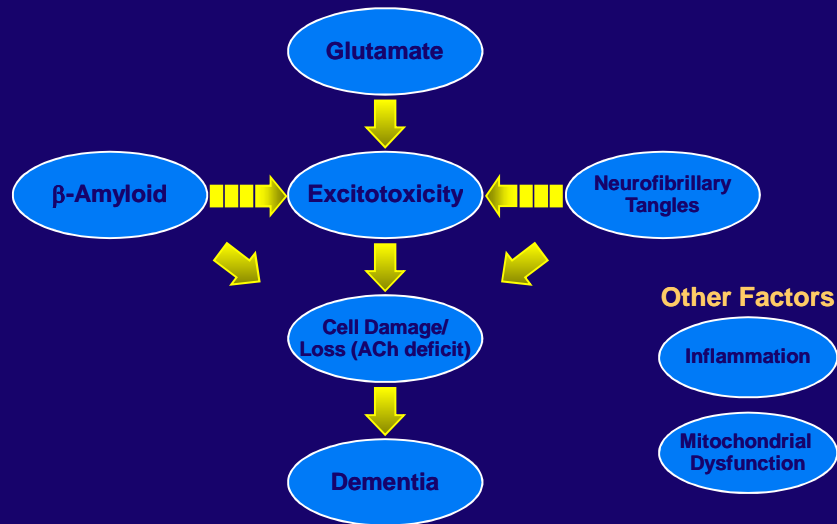
Neurofibrillary tangles^{1,2}

Tau & APOE4

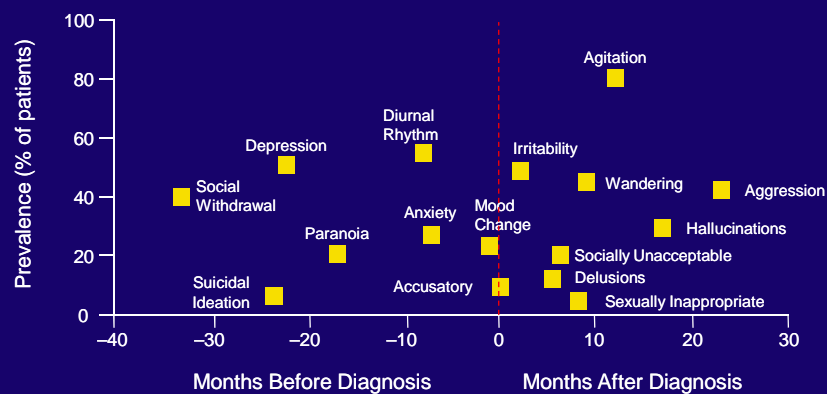
¹Wisniewski HM. In: Reisberg B, ed. *Alzheimer's Disease. The Standard Reference*. New York, NY:Free Press, Macmillan Publishing Co, Inc; 1983:57-61
²Iqbal I, Wisniewski HM. In:Reisberg B, ed. *Alzheimer's Disease. The Standard Reference*. New York, NY:Free Press, Macmillan Publishing Co, Inc; 1983:48-56
³Selkoe DJ. *The Genetics and molecular pathology of Alzheimer's Disease: roles of amyloid and presenilins*. *Neurologic Clinics* 18(4): Nov. 2000

Chromosome	Gene Defect	Phenotype
21	Beta APP mutations	Amyloidogenic A beta peptides
19	APOE4 polymorphism	Density of A beta plaques & vascular deposits
14	Presenilin 1 mutations	A beta 42 peptides
1	Presenilin 2 mutations	A beta 42 peptides
17	Tau mutation (absence of amyloid deposits)	Frontotemporal dementia with parkinsonism

Pathophysiologic Hypothesis of AD



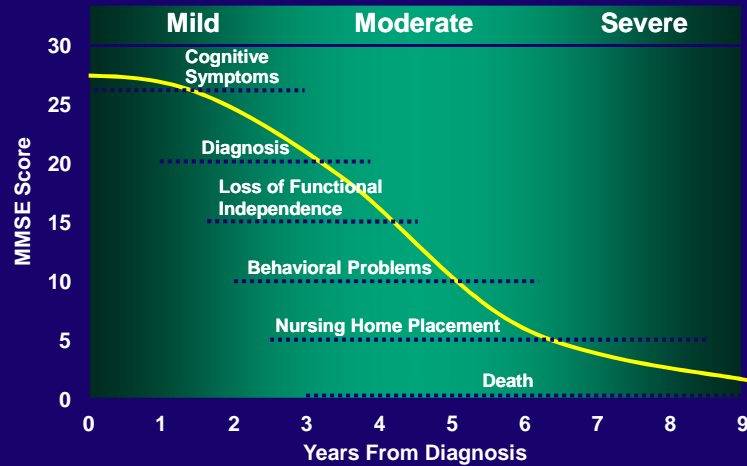
Peak Frequency of Behavioral Symptoms as Alzheimer's Disease Progresses



Jost BC, Grossberg GT. *J Am Geriatr Soc.* 1996;44:1078-1081.

Clinical Disease Progression

pragmatic stage = functional impairment + need for supervision



Reprinted from *Clinical Diagnosis and Management of Alzheimer's Disease*, H Feldman and S Gracon; Alzheimer's Disease: symptomatic drugs under development, pages 239-259, copyright 1996, with permission from Elsevier.

Cognition

All Capacities A Person Uses To Interact With The Internal And External World

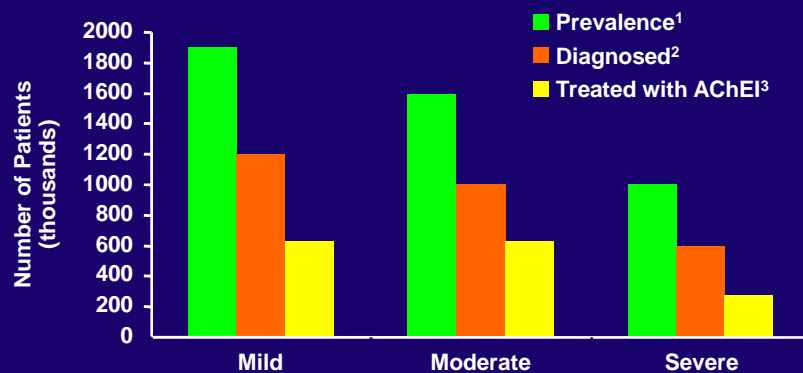
- Orientation
- Attention
- Memory
- Language
- Praxis
- Calculation
- Abstraction
- Sequencing
- Personality
- Judgement

Severity of Cognitive impairment =
functional impairment + need for supervision

Cognitive Disorders: The 6 D's

- Dementia
- Delirium
- Depression
- Damaged Brain
- Developmental Delay
- Deficient Education

Prevalence and Treatment Rates



Sources: 1. Hebert LE, Scherr PA, Bienias J, et al. *Arch Neurol.* 2003;60:1119-1122.
2. Datamonitor AD Treatment Algorithms. 2002.
3. Market Measures. 2003.

Diagnosis of AD

- Histology: gold standard
- Imaging techniques: promising
 - PET: Medicare reimbursed; registry completion required
 - [18F] FDG; bilateral temporoparietal hypometabolism*
 - [18F] FDDNP; localization and load of neurofibrillary tangles and beta-amyloid plaques
 - [11C] PIB localization and load beta-amyloid plaques
 - *Dementia: Medicare covers FDG-PET scans for either the differential diagnosis of fronto-temporal dementia (FTD) and Alzheimer's disease (AD) under specific requirements. Medicare has established specific requirements for coverage of the differential diagnosis of FTD and AD. These requirements are detailed in the NCD for Dementia and Neurodegenerative Diseases (220.6.1).
 - fMRI: medial temporal lobe activation; Hippocampal atrophy
 - SPECT: less temporal and spatial resolution than PET
- Blood / Chromosome testing: not AGS recommended
- Phenomenology (Hx+PE) & simple cognitive testing: commonly used in clinical practice
 - Disease present for decades prior to overt symptoms

Diagnostic Criteria

DSM IV TR

- Memory impairment &
- 1 or more cognitive dysfunctions
 - Aphasia
 - Apraxia
 - Agnosia
 - Executive function (planning, organizing, sequencing, abstracting)
- Impaired function
- Continuing decline
- Not due to other degenerative conditions
- Not exclusive to delirium

NINCDS-ADRDA

- Probable Alzheimer's Disease
 - 2 or more Cognitive deficits
 - Degeneration; ADL, IADL
 - No delirium / disorders
 - Onset 40 - 90 years of age
 - Behavioral abnormalities
- Possible Alzheimer's Disease
 - Dementia and no other neurologic, psychiatric, systemic disorders
- Uncertain / Unlikely Alzheimer's Disease
 - Sudden onset
 - Focal neurologic findings
 - Early seizures / gait disturbances

Common Domains of Diagnostic Criteria

- Cognitive Impairment 2 areas
- Functional Impairment
- Degeneration over time

Some Cognitive Screening Tests

- Mini-mental state examination (MMSE)
- Clock drawing task
- Functional activities questionnaire
- Recall of a five-item name and address +one-minute verbal fluency for animals
- Alzheimer's Disease Assessment Scale (ADAS)
- Brief Screen for Cognitive Impairment (BSCI)

DEMENTIA SCREENING TOOL
Functional Changes in Instrumental Activities of Daily Living (IADLs) over Time

Byron Bair, MD SLC VAMC-University of Utah

Change in past 5 years		
YES	NO	<u>Within the Home</u>
		Cooking
		Housecleaning
		Laundry
		Medication management
		Telephone use
		Finance management
		Other activity change
		<u>Outside of Home</u>
		Shopping (food, drugs, clothes)
		Transportation (driving, traffic tickets, bus use)
		Making appointments
		Social events
		Religious activity
		Other activity change

Any change over the past 5 years indicates the need for further evaluation concerning cognitive function

Diagnostic Evaluation

- History: Medications/Drugs
- Screens: MMSE, clock drawing, GDS etc.
- Physical Exam; Ortho BP's, rectal, ROM etc.
- Selected Labs: Lytes, CBC diff, UA, PVR, ABG, TFT's, B12, Folate, FTA, Toxic Screen, Drug Level, EKG, Chest X-Ray
- Consider: brain imaging, LP, chromosome identification

Treatment Considerations

- Treat Underlying Disorders
- Consider Delirium & Depression
- Avoid “Low Spinal Reflexes”
- Use Multidisciplinary Teams
- Determine Operationally Defined Targets
- Monitor Targets For Efficacy of Treatments
- Use Multiple Modalities Simultaneously

Treatments For Alzheimer’s

- Non-Pharmacological Interventions
- Pharmacological Agents
 - FDA Approved Agents
 - Non-FDA Approved Agents
- Agents Targeting Behavior

Alzheimer's Treatment: Non-Pharmacological Models

- Environmental
 - appropriate levels of supervision & structure
 - physical location: 24 hour supervision
 - modify sensory stimuli
 - low in evening, higher during day: music, walks, activities
 - TV: news, appropriate content
- Psychosocial
 - validation therapy
 - reminiscence therapy
- Physical Restraints

Pharmacological Treatment

- Symptom treatment
 - Cognition
 - Function
 - Behavior
 - Care giver burden
- Disease modification
 - Prevent
 - Stabilize
 - Reverse process
- Track Symptoms
 - Scales / testing
 - Various Standardized
 - Global impression
 - “Trained” observation
- Track Disease
 - Imaging
 - PET
 - [18F] FDDNP; localization & load of neurofibrillary tangles and beta-amyloid plaques
 - [11C]PIB localization & load beta-amyloid plaques
 - Other methods?

FDA Approved Agents

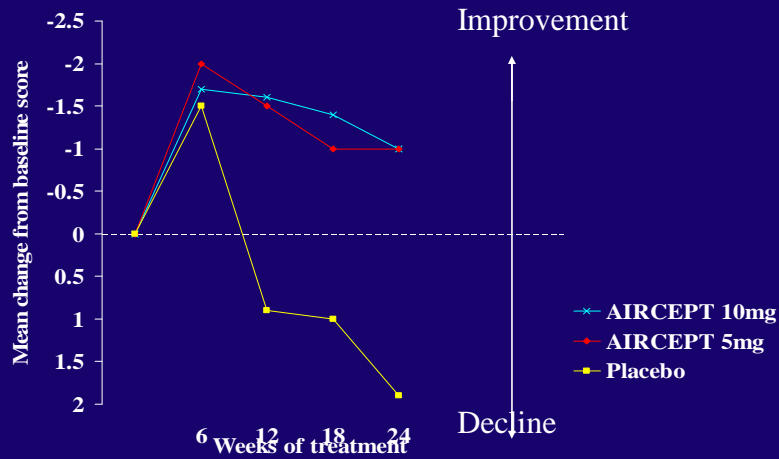
- All approved for “symptomatic” treatment of AD
- Cholinesterase Enzyme Inhibitors (ChEI)
 - Mild to moderate stages
- NMDA receptor modifiers (memantine)
 - Moderate to severe stages
 - Approved for use as a single or dual agent with ChEI
- Not FDA approved for other dementias
 - Vascular , Parkinson’s, Lewy Body, Mixed, Frontotemporal
 - Emerging literature

Cholinesterase Inhibitors: General Overview

	Tacrine	Donepezil	Rivastigmine	Galantamine
Year available	1993	1996	2000	March 2001
Brain selectivity	No	Yes	Yes	Yes
Reversibility	Reversible	Reversible	Reversible	Reversible
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Enzymes inhibited				
AChE	Yes	Yes	Yes	Yes
BuChE	Yes	Negligible	Yes	Negligible

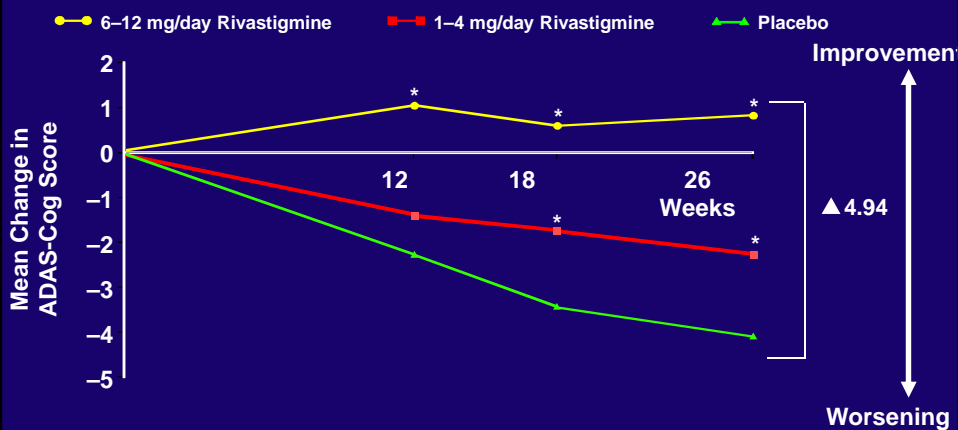
AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; NDA = new drug application.
Physicians' Desk Reference® 2000; Nordberg A, Svensson AL. *Drug Safety*. 1998;19:465-480.
 Weinstock M. *CNS Drugs*. 1999;12:307-323; Enz A, et al. *Prog Brain Res*. 1993;98:431-438.

DONEPEZIL HCl (ARICEPT™) ADAS-cog*28



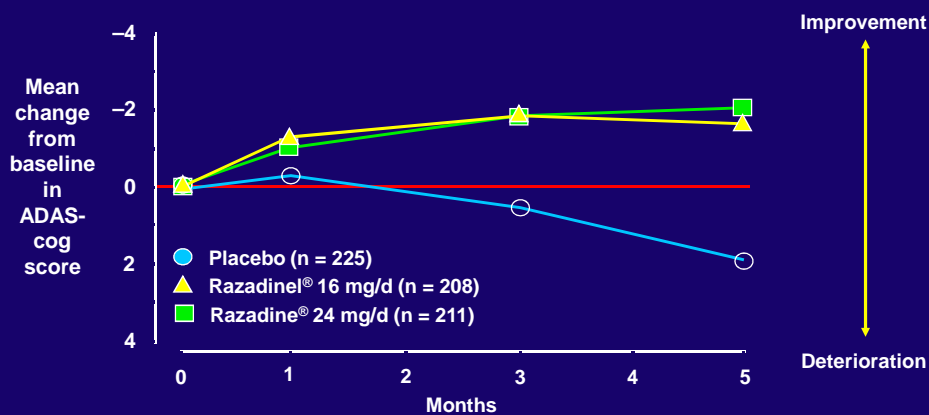
*In one controlled clinical trial of 30 weeks duration in 473 patients, 154 patients were randomly assigned to receive daily doses of 5 mg. One hundred fifty-seven patients were randomly assigned to receive daily doses of 10 mg. One hundred sixty-two patients were randomized to placebo. The 30-week trial was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period.

Rivastigmine (Exelon): Mean Change From Baseline in ADAS-cog†



Corey-Bloom J et al, for the ENA 713 B352 Study Group. *Int J Geriatr Psychopharmacol.* 1998;1:55-65.

Galantamine (Razadine): Mean Change From Baseline in ADAS-cog



* $P < .001$ vs placebo.

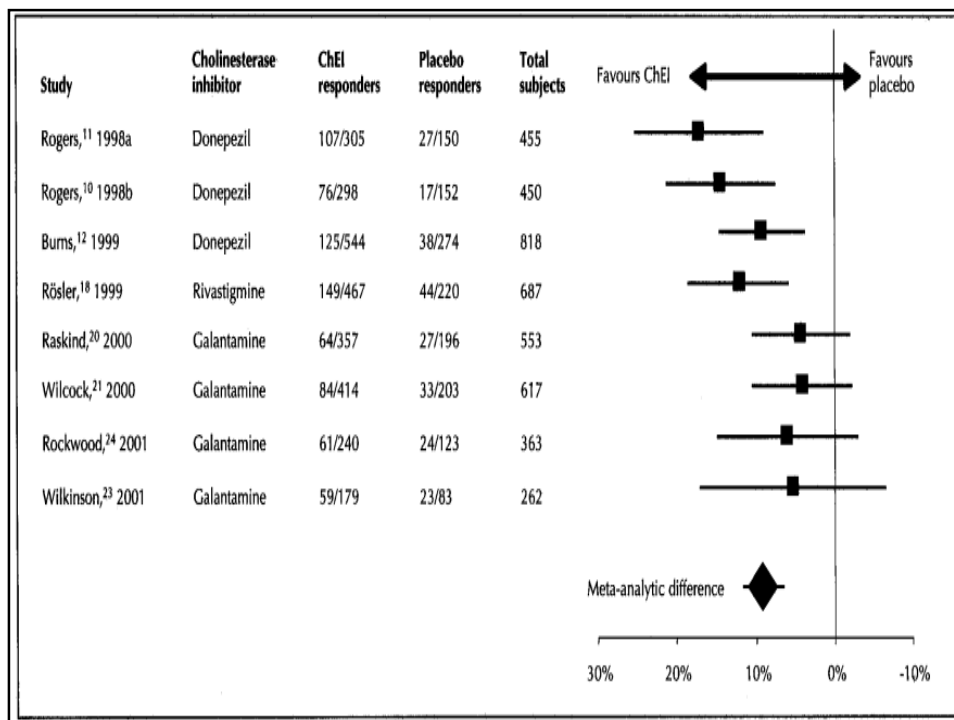
Tariot PN et al. *Neurology*. 2000;54:2269-2276.

Efficacy and safety of cholinesterase inhibitors in AD: a meta-analysis CMAJ 169(6) Sept 16, 2003

- 16 randomized, double-blind, placebo-controlled, parallel-group trials of ChEI
- 5159 patients on one of three agents (donepezil, rivastigmine, galantamine)
- 2795 patients on placebo

First author, publication year	ChEI studied; doses; duration of treatment	No. of subjects randomly assigned, total (ChEI, placebo), no. of subjects completing study	Scales(s) used to assess response†	Jadad quality score‡
Rogers, ¹¹ 1996	Donepezil; 1, 3, 5 mg/d; 12 wk	161 (121, 40), 141	ADAS-cog, CGIC, MMSE	4
Rogers, ¹¹ 1998a	Donepezil; 5, 10 mg/d; 12 wk	468 (315, 153), 412	ADAS-cog, CDR-SB, CIBIC+, MMSE, QoL	4
Rogers, ¹⁰ 1998b	Donepezil; 5, 10 mg/d; 24 wk	473 (311, 162), 368	ADAS-cog, CDR-SB, CIBIC+, MMSE, QoL	5
Burns, ¹² 1999	Donepezil; 5, 10 mg/d; 24 wk	818 (544, 274), 631	ADAS-cog, CDR-SB, CIBIC+, IDDD	4
Winblad, ¹³ 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 52 wk	286 (142, 144), 192	ADL, GBS, GDS, MMSE, NPI	5
Homma, ¹⁴ 2000	Donepezil; 5 mg/d; 24 wk	263 (134, 129), 228	ADAS-Jcog, CDR-SB, CMCS, J-CGIC, MENFIS	4
Mohs, ¹⁵ 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 54 wk	431(217, 214), 111	ADFACS, CDR-SB, MMSE	5
Feldman, ¹⁶ 2001	Donepezil; 5 mg/d for 28 d, then 10 mg/d, for total of 24 wk	290 (144, 146), 247	CIBIC+, DAD, FRS, MMSE, NPI, SIB	5
Agid, ¹⁷ 1998	Rivastigmine; 4, 6 mg/d; 13 wk	402 (269, 133), 357	CGIC	5
Rösler, ¹⁸ 1999	Rivastigmine; 1-4, 6-12 mg/d; 26 wk	725 (486, 239), 581	ADAS-cog, CIBIC+, GDS, MMSE, PDS	5
Corey-Bloom, ¹⁹ 1998	Rivastigmine; 1-4, 6-12 mg/d; 26 wk	699 (464, 235), 545	ADAS-cog, CIBIC+, GDS, MMSE	5
Raskind, ²⁰ 2000	Galantamine; 24, 32 mg/d; 6 mo	636 (423, 213), 438	ADAS-cog, CIBIC+, DAD, MMSE	5
Wilcock, ²¹ 2000	Galantamine; 24, 32 mg/d; 6 mo	653 (438, 215), 525	ADAS-cog, CIBIC+, DAD	5
Tariot, ²² 2000	Galantamine; 8, 16, 24 mg/d; 5 mo	978 (692, 286), 779	ADAS-cog, ADCS/ADL, CIBIC+, NPI	5
Rockwood, ²⁴ 2001	Galantamine; 24, 32 mg/d; 3 mo	386 (261, 125), 288	ADAS-cog, CIBIC+, DAD, NPI	5
Wilkinson, ²³ 2001	Galantamine; 18, 24, 36 mg/d; 3 mo	285 (198, 87), 206	ADAS-cog, CGIC, PDS	5

*Except in the study of Feldman and coworkers, who studied treatment of moderate to severe dementia.
†ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADAS-Jcog = Alzheimer's Disease Assessment Scale-cognitive subscale, Japanese version; ADCS/ADL = AD Cooperative Study Activities of Daily Living; ADFACS = AD Functional Assessment and Change Scale; ADL = Activities of Daily Living; CDR-SB = Clinical Dementia Rating-Sum of the Boxes; CGIC = Clinical Global Impression of Change; CIBIC+ = Clinician's Interview-Based Impression of change plus caregiver input; CMCS = Caregiver-rated Modified Crichton Deterioration in Daily Living Activities in Dementia; J-CGIC = Japanese version of CGIC; MENFIS = Mental Function Impairment Scale; IDDD = Modified Interview for Deterioration in Daily Living Activities in Dementia; I-CGIC = Japanese version of CGIC; MENFIS = Mental Function Impairment Scale; MMSE = Mini-Mental Status Examination; NPI = Neuropsychiatric Inventory; PDS = Progressive Deterioration Scale; QoL = Quality of Life; SIB = Severe Impairment Battery.



Efficacy and safety of cholinesterase inhibitors in

AD: a meta-analysis CMAJ 169(6) Sept 16, 2003

Pooled results

- NNT global response = 12 (95% CI=9-16)
- NNT cognitive response = 10 (95% CI=8-15)
- NNH adverse event = 12 (95% CI=10-18)
- NNH dropout = 13 (95% CI=11-17)
- NNH dropout due to adverse event = 16 (95% CI = 13-19)
- All individual agents showed efficacy over placebo

Compare: 5 yr Tx of HTN to prevent one MI, CVA, death

- NNT 29-86

Efficacy and safety of cholinesterase inhibitors

in AD: a meta-analysis CMAJ 169(6) Sept 16, 2003

- Donepezil (3 trials)
 - NNT: 8 (95% CI 6-12)
 - Excess proportion: 13% (95% CI 8-17%)
- Galantamine (4 trials)
 - NNT: 22 (95% CI 12-157)
 - Excess proportion: 5 (95% CI 1-8%)
- Rivastigmine (1 trial)
 - NNT ?
 - Excess proportion: 12 (95% CI 10-18%)

Long Term Donepezil treatment in 565 patients with AD(AD2000): randomised double-blind trial

Lancet; 26Jun 2004; 363(9427):2105-15

- National Health Service sponsored
- Inclusion: clinical dx of AD (no stage specified) + clinical uncertainty of benefit from treatment
- Exclusion: none
- 486 completed preliminary 12 wk randomization
- Primary endpoints:
 - Institutionalization care
 - Function; loss of 2/4 ADL's or 6/11 IADL's
- Secondary endpoints:
 - MMSE

Long Term Donepezil treatment in 565 patients with AD(AD2000): randomised double-blind trial

Lancet; 26Jun 2004; 363(9427):2105-15

- Results
- Year 2
 - Function (BADL) 1.0 better (95%CI 0.5-1.6; p<0.0001)
 - MMSE = 0.8 points better (95%CI 0.5-1.2; p<0.0001)
- Year 3
 - No difference in institutionalization
 - No difference in function
- Author conclusion: donepezil is not cost effective

Anticholinesterases: What To Expect

- Positive treatment effects shown for symptoms
 - Magnitude debated
 - Impact: cognition, function, behavior, caregiver burden
 - Full impact may require 3 months @ effective dose
 - Improve / slow / stabilize symptoms for 1-2 years
 - Delay ECF placement 2-3 years?
- Impact on disease modification?
 - Studies pending
- Agents are not equivalent
 - Head to head trials?: try other agents if one “fails”
- Cost effectiveness debated

Anticholinesterases: What To Expect

- Nausea and vomiting & GI side-effects
 - class characteristic; may be transient
 - worse with BuChE receptor activity?
 - take after meals
- How to Start
 - Aricept (donepezil): 5mg x 4wk then 10mg
 - Exelon (rivastigmine): 1.5mg-3mg-4.5mg-6mg q2wk
 - Razadine (galantamine) 4mgbid x 1 mo - 8mg - 12mg
- When to Start & Stop?

Memantine (Namenda)

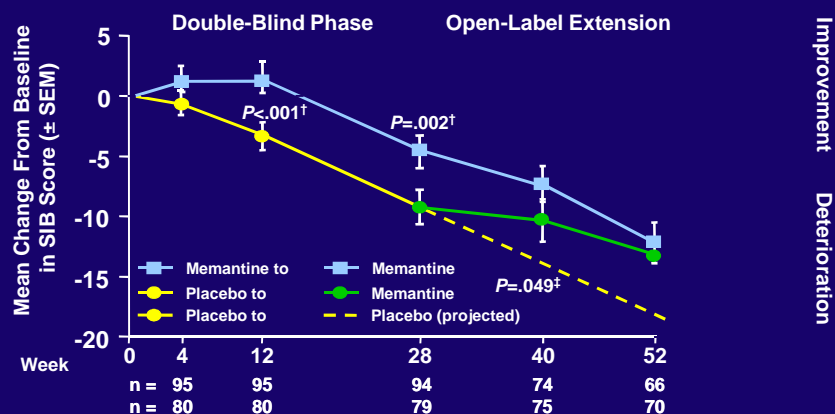
- Different action than ChEI: NMDA / glutamate
- FDA approved for Moderate To Severe dementia
 - Mono-therapy: effect seen 12-28 weeks
 - adjunct therapy: effect seen 4 weeks
 - Severe ECF patients: effect seen in 1-4 weeks (low dose)
 - Movement, toileting & participation in activities
 - Effective: function, cognition, global impression, behavior
- CP450 friendly & 100% bioavailable
- Renal excretion
- Antagonistic effects at the 5HT₃ receptor
- Side-effect profile as monotherapy similar to placebo

Memantine Trials

<i>Study Design</i>	<i>Monotherapy in Moderate to Severe AD¹</i>	<i>Combination Memantine and Donepezil²</i>	<i>Nursing Home Patients With Dementia³</i>
Memantine dose	10 mg bid	10 mg bid (plus donepezil)	10 mg qd
Duration in weeks	28	24	12
MMSE range	3-14	5-14	<10
<i>Principal Efficacy Measures</i>			
Global change	CIBIC-Plus	CIBIC-Plus	CGI-C
Cognition	SIB	SIB	
Function	ADCS-ADL₁₉	ADCS-ADL₁₉	BGP-Care

1. Reisberg B, et al. *N Engl J Med.* 2003;348:1333-1341.
 2. Tariot P, et al. *JAMA.* 2004;291:317-324.
 3. Winblad B, et al. *Int J Geriatr Psychiatry.* 1999;14:135-146.

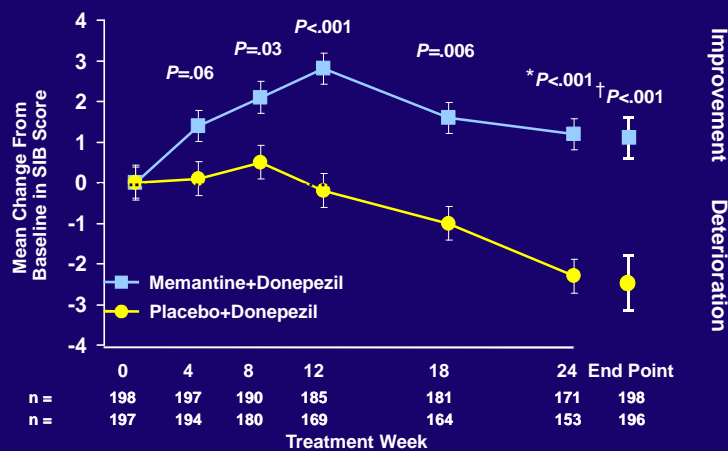
Memantine monotherapy Results: Cognition—SIB*



*OC analysis; †Memantine vs placebo; ‡Rate of decline between placebo group (weeks 1-28) and placebo-memantine group (weeks 28-52).

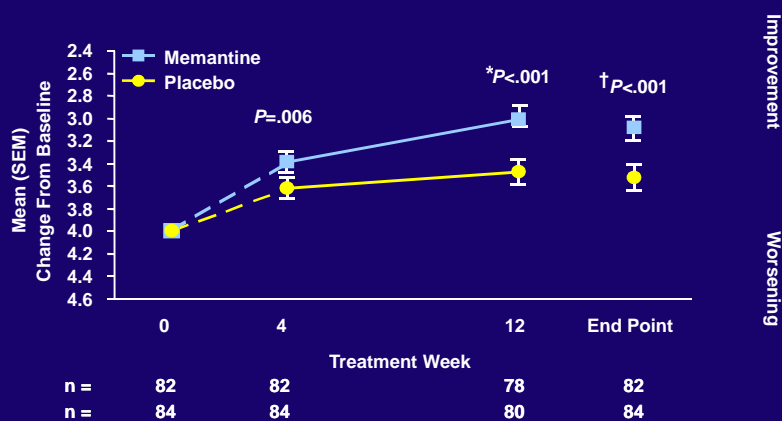
Sources: Ferris S, et al. Presented at the 16th Annual Meeting of the American Association for Geriatric Psychiatry; March 1-4, 2003; Honolulu, Hawaii. Data on file, Forest Laboratories, Inc.

Memantine+Donepezil Results: Cognition—SIB



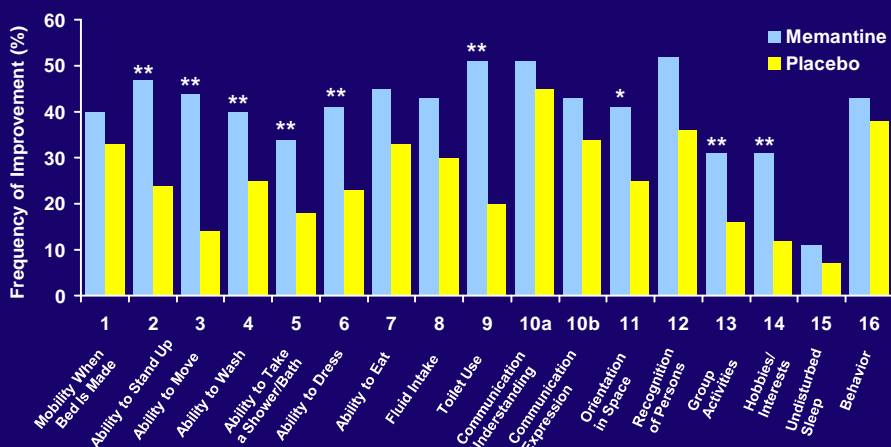
*OC analysis. †LOCF analysis.
Adapted from Tariot P, et al. *JAMA*. 2004;291:317-324.

Memantine Severe Dementia ECF Results: Global Change—CGI-C



*OC analysis. †LOCF analysis.
Source: Winblad B, et al. *Int J Geriatr Psychiatry*. 1999;14:135-146.

Memantine Severe Dementia ECF Results : Function—D-Test



OC analysis, n=151.
*Trend to treatment difference. Assessed by Wilcoxon rank sum test on the detailed scale of change (P < .10).
**Statistically significant treatment difference (P < .05).
Adapted from Winblad B, et al. *Int J Geriatr Psychiatry*. 1999;14:135-146.

Memantine (Namenda)

- How to start (per FDA)
 - 5mg x 1 week
 - 5mg bid x 1 week
 - 10mg am & 5mg pm x 1 week
 - 10mg bid thereafter
 - “severe” renal impairment = 5mg bid
 - Cockcroft-Gault CrCl = 5-29mL/min
- When to Start & Stop?

Dementia Treatments Summary

- The data: Aesop’s blind men and the elephant
- AD / Dementia is heterogeneous
 - Statistics vs individuals: track individual response
 - Long term results: most trial duration = 6 months with placebo
- Single therapy: ChEI or memantine
 - ChEI have positive effect:
 - CMAJ 169(6) Sept 16, 2003
 - Cost effectiveness of ChEI disputed:
 - Lancet Jun 26, 2004; 363(9427):2105-15 vs others (National Health service vs Industry)
 - Memantine has positive effect & additive to ChEI
- Dual therapy: ChEI + memantine
 - May provide greater impact
- How to implement clinically?

Dementia Treatments: Clinical implementation

- Possible Answer:
 - Select patients for continued treatment by clinical response
 - Clinical response tracked by care provider/s to determine if impact is clinically “significant” or important
 - Clinical Response Tracking Sheet: education + impact + compliance
 - Dementia treatment clinic pilot:
 - When to begin & Which agent to start first, unresolved by data
- Until better data is available:
 - 3 month trial on dual agents @ effective doses
 - Already on ChEI = add memantine
 - New treatment = start memantine then add ChEI
 - Improvement = stay on therapy
 - Decline = trial of monitored discontinuation and re-initiate if clinically important decline appears
 - Stable at 3 months = 3 month treatment extension to determine improvement or decline and re- assess diagnosis
- Key: structured monitoring + planned / monitored discontinuation
- Need clinical trial to verify this approach

CLINICAL RESPONSE TRACKING SHEET																		
<small>BYRON BAIR MDSALT LAKE CITY GRECC COLLABORATIVE STUDY</small>																		
WEEKLY FLOW CHART																		
CATEGORIES	Place the global impression of clinical response noted from the weekly evaluation of each category in the columns provided. No change = 0; Improvement = +1,+2,+3; Decline = -1,-2,-3																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
MEMORY <small>Remembering names and events, recognizing friends and family, remembering instructions</small>																		
COMMUNICATION <small>Taking part in conversation, understanding, ability to find appropriate words</small>																		
SENSE OF TIME AND PLACE <small>Keeping track of time (day, year, season), knowing place (where they are), ability to find way around home or community</small>																		
BASIC ACTIVITIES OF DAILY LIVING <small>Eating, dressing, grooming, using the bathroom</small>																		
HOUSEHOLD TASKS AND HOBBIES <small>Shopping, handling money, cooking, cleaning, using appliances/phone, setting the table, interest in hobbies/social events</small>																		
MOOD AND BEHAVIOR <small>Sadness, anger, irritability, hallucinations, inappropriate behavior, lack of interest in things</small>																		
OTHER COGNITIVE FUNCTION																		
PHYSICIAN GLOBAL ASSESSMENT <small>Place assessment of patient's overall status (-3, -2, -1, 0, +1, +2, +3)</small>																		