2007 KCGP 추계 학술대회, 서울아산병원 정신과 김성윤

DEVELOPMENT OF DRUGS FOR ALZHEIMER'S DISEASE

Phase of Clinical Trials

- Phase I trials:
  - Experimental drug or treatment in a small group of people (20-80)
  - Safety, Safe dosage range, Side effects
- Phase II trials:
  - A larger group of people (100-300)
  - Efficacy and further evaluation of the safety
- Phase III trials:
  - Large groups of people (1,000-3,000) to confirm its effectiveness, monito r side effects, compare it to commonly used treatments
- Phase IV trials:
  - Post marketing studies
  - Additional information: drug's risks, benefits, and optimal use

신약개발과 임상시험

~5000 targets / 3~4 yr / 100~200M $

50~100 targets / 1~2 yr / 50~150M $

연구/개발 | 후보물질 | 전임상시험 | 연구용 신약

- **Create Development Candidate**
  - Target ID
  - Lead Generation & Optimization

- **Evaluate Activity and Safety Profiles in Animals**
  - Compound Scale-Up / Formulation Development
  - Toxicity and Pharmacology Studies
  - PK/Metabolism Studies

5~10 targets / 6~7 yr / 150~350M $

1 target / 0.5~2 yr

임상시험 | 신약인정 | 시판허가 | 시판

- **Evaluate Efficacy and Safety in Humans**

- **Agency Review**

Phase I Tolerance PK

Phase IIa Pilot test

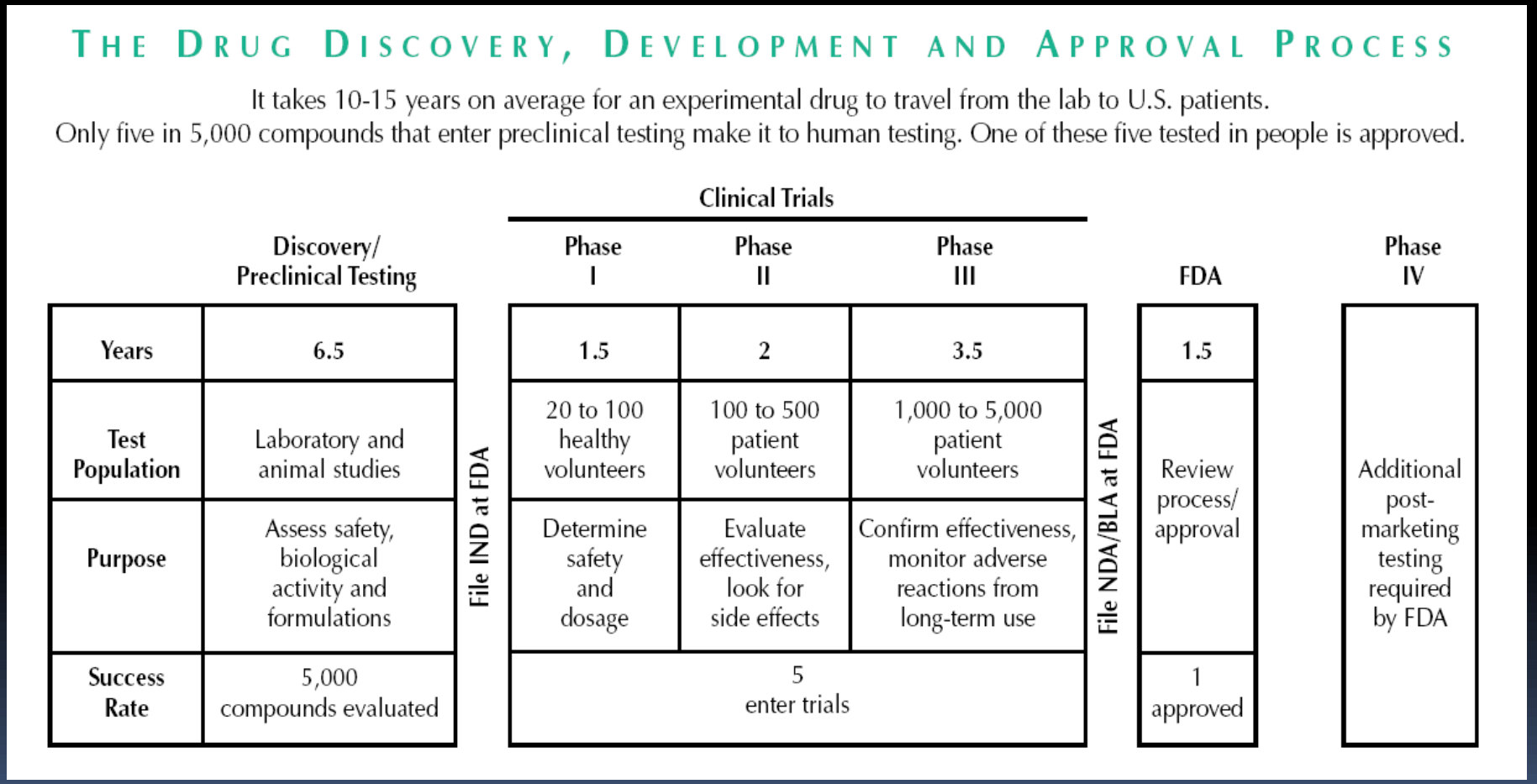
Phase IIb Dose/ Response

Phase IIIa Therapeutic Dose / PI

Phase IIIb Differentiation/ Marketing Adv

Phase IV PMS Regulatory Req Marketing

Drug Approval Process



The Drug Discovery, Development and Approval Process

It takes 10-15 years on average for an experimental drug to travel from the lab to U.S. patients.
Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

	Discovery/ Preclinical Testing		Clinical Trials: Phase I	Clinical Trials: Phase II	Clinical Trials: Phase III		FDA		Phase IV
Years	6.5		1.5	2	3.5		1.5		
Test Population	Laboratory and animal studies	File IND at FDA	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	File NDA/BLA at FDA	Review process/ approval		Additional post-marketing testing required by FDA
Purpose	Assess safety, biological activity and formulations		Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

2005 Medicine in Development, PhRMA

R&D Expenditure and Trials

Selected companies ranked by health-care R&D expenditure		
Company	R&D Spend (2005 $milliions)	Recruiting trials
Pfizer Inc.	$7,256	311
GlaxoSmithKline Plc.	$5,495	350
Sanofi-Aventis	$4,949	246
Novartis	$4,372	355
Roche	$4,001	160
Merck & Co.	$3,848	143
AstraZeneca Plc.	$3,314	194
Eli Lilly and Co.	$2,940	209
Wyeth	$2,722	174
Bristol-Myers Squibb Co.	$2,513	193
Amgen Inc.	$2,302	90
Schering-Plough Corp.	$1,762	62
Boehringer Ingelheim GmbH	$1,544	69
Takeda Chemical Industries Ltd.	$1,507	22
Daiichi-Sankyo	$1,340	24
Astellas	$1,291	37
Abbott Laboratories	$1,140	67
Schering AG	$1,019	23

Source: 2005 Clinicaltrials.gov

Donepezil: RCT

A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease

S.L. Rogers, PhD; M.R. Farlow, MD; R.S. Doody, MD, PhD; R. Mohs, PhD; L.T. Friedhoff, MD, PhD; and the Donepezil Study Group*

Article abstract—The efficacy and safety of donepezil as a treatment for patients with mild to moderate Alzheimer's disease (AD) was investigated in a multicenter, double-blind study. Patients were randomly assigned to treatment with placebo (n = 162), 5 mg/d donepezil (n = 154), or 10 mg/d donepezil (n = 157) for 24 weeks followed by a 6-week, single-blind placebo washout. The primary efficacy measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Assessment of Change-Plus (CIBIC plus), with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale-Sum of the Boxes (CDR-SB), and patient rated Quality of Life (QoL) used as secondary measures. Cognitive function, as measured by the ADAS-cog, was significantly improved in the 5- and 10-mg/d donepezil groups as compared with the placebo group at weeks 12, 18, and 24. Clinician's global ratings on the CIBIC plus also improved in both the 5- and 10-mg/d donepezil groups relative to placebo. At the end of the 6-week placebo washout phase, ADAS-cog scores and CIBIC plus ratings were not significantly different for the three groups. Significant treatment benefits were also observed consistently in both the 5- and 10-mg/d groups on the MMSE and the CDR-SB, but there was no consistent effect on the patient-rated QoL. Cholinergic side effects (primarily diarrhea, nausea, and vomiting) were reported more often in the 10-mg/d group than either the 5-mg/d or placebo groups. Side effects were transient and generally mild in severity. These data indicate that donepezil is a well-tolerated drug that improves cognition and global function in patients with mild to moderate AD.

NEUROLOGY 1998;50:136–145

Rogers et al., 1998, Neurology

Donepezil: RCT

- Multicenter, double-blind study on mild to moderate AD subjects
- 5mg (154), 10mg (157), placebo (162)
- 24 weeks
- Primary:
  - ADAS-cog, CIBIC-Plus
- Secondary:
  - MMSE, CDR-SB, QoL (Pt)
- Result:
  - Cognition, CIBIC-Plus improved in 12, 18, 24 week (5, 10mg)
  - MMSE, CDR-SB also improved, but not on QoL

Rogers et al., 1998, Neurology

Rivastigmine: RCT

Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial

Michael Rösler, Ravi Anand, Ana Cicin-Sain, Serge Gauthier, Yves Agid, Peter Dal-Bianco, Hannes B Stähelin, Richard Hartman, Marguirguis Gharabawi on behalf of the B303 Exelon Study Group

Abstract

Objectives To assess the effects of rivastigmine on the core domains of Alzheimer's disease.
Design Prospective, randomised, multicentre, double blind, placebo controlled, parallel group trial. Patients received either placebo, 1-4 mg/day (lower dose) rivastigmine, or 6-12 mg/day (higher dose) rivastigmine. Doses were increased in one of two fixed dose ranges (1-4 mg/day or 6-12 mg/day) over the first 12 weeks with a subsequent assessment period of 14 weeks.
Setting 45 centres in Europe and North America.
Participants 725 patients with mild to moderately severe probable Alzheimer's disease diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

Introduction

One of the most successful treatments for Alzheimer's disease has been the use of acetylcholinesterase inhibitors to enhance surviving cholinergic neurotransmission by inhibiting the breakdown of released acetylcholine. The first of these drugs approved for treating Alzheimer's disease, tacrine, is effective but can cause an increase in liver enzyme concentrations; in some countries, such as in the United Kingdom, this has prevented it from being licensed.[1–3] More recently, a second acetylcholinesterase inhibitor, donepezil (a piperidine derivative) has become available.[4 5] Clinical trials have reported benefits on cognition and global evaluations.[4 5] Rivastigmine is a novel, "pseudo-irreversible," brain selective inhibitor of acetylcholinesterases, the metabolism of which is almost totally

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disease. This is the first treatment to show compelling evidence of efficacy in a predominantly European population.

Roesler et al., 1999, BMJ

Rivastigmine: RCT

- Prospective, randomized, multicenter, double-blind, placebo-controlled, parallel group trial
- Placebo, 1~4mg/day, 6~12mg/day: 12 + 14 weeks
- 45 centers in Europe and North America
- 725 subjects with mild to moderate AD by DSM-IV and NINCDS-ADRDA
- Primary:
  - ADAS-cog, CIBIC-plus, PDS (Progressive deterioration scale)

Roesler et al., 1999, BMJ

Rivastigmine: RCT

Table 1 Instruments used to evaluate the efficacy of rivastigmine in treating Alzheimer's disease

Instrument	Symptoms or domains assessed	Source of information	Range of scale and interpretation
Alzheimer's disease assessment scale (cognitive subscale)	Cognition (memory, language, orientation, praxis)	Patient	0-70 points 0=no errors (rarely achieved, even in general population) 70=severe impairment
Clinician interview based impression of change scale (incorporating caregiver information)	Global assessment of behaviour, general psychopathology, cognition, and activities of daily living	Patient and caregiver during interview with clinician*	1-7 points 1, 2, 3=marked, moderate, or minimal improvement 4=no change 5, 6, 7=minimal, moderate, or marked deterioration
Progressive deterioration scale	Activities of daily living (dressing and eating independently, social interaction, participation in housework and hobbies, awareness of time, handling of financial matters)	Caregiver	29 items Scores range from 0 to 100

*Clinicians had no access to data on efficacy or safety.

Roesler et al., 1999, BMJ

Rivastigmine: RCT

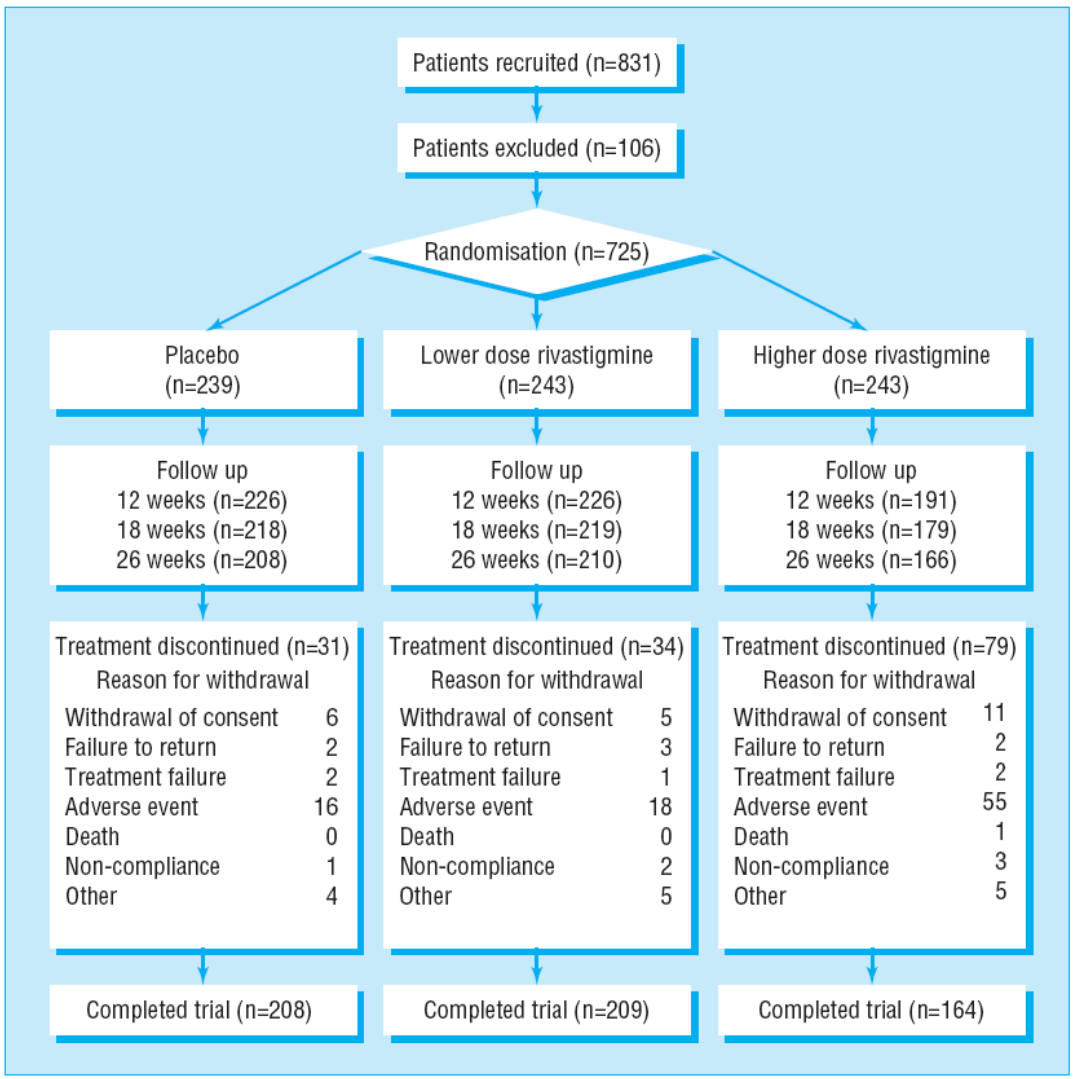

Fig 1 Outcome of allocation to treatment and reasons for withdrawal from the study

Roesler et al., 1999, BMJ

Galantamine: RCT

Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease

D. Wilkinson[1]* and J. Murray[2] in collaboration with the Galantamine Research Group*†

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[2]*Business Development Director, Shire Pharmaceuticals, Andover, UK*

SUMMARY

Objectives To investigate whether Galantamine significantly improves the core symptoms of Alzheimer's disease (AD)
Background Galantamine is a reversible, competitive, selective inhibitor of acetylcholinesterase (AChE) that also allosterically modulates nicotinic acetylcholine receptors. This dual mechanism of action provided the rationale for a phase II trial of galantamine in AD.
Method A multicentre, randomized, parallel, double-blind, placebo-controlled trial was carried out to evaluate the efficacy and tolerability of galantamine 18, 24 and 36 mg/day administered for 3 months in 285 patients with mild-to-moderate probable AD. The primary outcome measure was the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog); secondary outcome measures were the Clinical Global Impression of Change (CGIC) and the Progressive Deterioration Scale (PDS).
Results Patients treated with galantamine 24 mg/day had a significantly better outcome than placebo on ADAS-cog; the treatment difference was 3 points on the intention-to-treat (ITT) analysis ($p = 0.01$) and 4.2 points on per protocol analysis ($p = 0.001$). Per protocol analysis showed that galantamine had a significantly better outcome than placebo on PDS (24-mg/day dose, $p < 0.05$) and CGIC (36-mg/day dose, $p < 0.05$). Galantamine was well tolerated at the lower doses of 18 and 24 mg/day where it produced mild, transient effects typical of cholinomimetic agents.
Conclusion This study shows that, relative to placebo, galantamine significantly improves the core symptoms of Alzheimer's disease.

KEY WORDS — Galantamine; dementia; Alzheimer's disease; acetylcholinesterase inhibitor

Wilkinson et al., 2001, Int J Geriat Psychiatry

Galantamine: RCT

- Phase II trial of galantamine in AD
- Multicenter, randomized, parallel, double-blind, placebo-controlled RCT
- 285 subjects, 3 months, 18, 24, 36 mg/d
- Primary:
  - ADAS-cog
- Secondary:
  - CGIC and PDS (progressive deterioration scale)

Wilkinson et al., 2001, Int J Geriat Psychiatry

Galantamine: RCT

Table 2. Efficacy outcomes after 12 weeks

Assessment	Placebo group		Galantamine 18 mg/day group		Galantamine 24 mg/day group		Galantamine 36 mg/day group		
ADAS-cog: mean (SEM) change from baseline	ITT (LOCF) ($n=82$) 1.6 (0.7)	PP ($n=53$) 2.3 (0.9)	ITT (LOCF) ($n=81$) −0.1 (0.7)	PP ($n=62$) −0.8* (0.8)	ITT (LOCF) ($n=55$) −1.4** (0.9)	PP ($n=44$) −1.9** (1.0)	ITT (LOCF) ($n=51$) −0.7† (0.7)	PP ($n=29$) −1.8** (0.9)	
CGIC: n (%)	($n=83$)	($n=74$)	($n=79$)	($n=61$)	($n=53$)	($n=44$)	($n=47$)	($n=29$)	
Much improved	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)	2 (4.5)	0 (0.0)	0 (0.0)	*
Improved	23 (31.3)	25 (33.8)	29 (36.7)	27 (44.3)	13 (24.5)	13 (29.5)	15 (31.9)	14 (48.3)	
No change	34 (41.0)	28 (37.8)	38 (48.1)	24 (39.3)	29 (54.7)	21 (47.7)	26 (55.3)	13 (44.8)	
Worse	23 (27.7)	21 (28.4)	12 (15.2)	10 (16.4)	9 (17.0)	8 (18.2)	6 (12.8)	2 (6.9)	
Much worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PDS-1: n (%)	($n=87$)	($n=74$)	($n=88$)	($n=62$)	($n=56$)	($n=44$)	($n=54$)	($n=29$)	
Much worse	7 (8.0)	3 (4.1)	4 (4.5)	1 (1.6)	1 (1.8)	0 (0.0)	1 (1.9)	1 (3.4)	
Worse	15 (17.2)	13 (17.6)	12 (13.6)	9 (14.5)	5 (8.9)	2 (4.5)	11 (20.3)	5 (17.2)	
No change	57 (65.5)	50 (67.6)	61 (69.3)	43 (69.4)	42 (75.0)	34 (77.2)	38 (70.4)	19 (65.5)	*
Improved	8 (9.2)	8 (10.8)	9 (10.2)	7 (11.3)	7 (12.5)	7 (15.9)	4 (7.4)	4 (13.8)	
Much improved	0 (0.0)	0 (0.0)	2 (2.3)	2 (3.2)	1 (1.8)	1 (2.3)	0 (0.0)	0 (0.0)	

SEM, standard error of mean; ITT, intention-to-treat analysis; LOCF, last-observation-carried-forward method; PP, per protocol analysis; ADAS-cog, Alzheimer's Disease Assessment Scale cognitive subscale; CGIC, Clinical Global Impression of Change; PDS-1, Progressive Deterioration Scale. *$p<0.05$, **$p<0.01$, †$p=0.08$ versus placebo.

Wilkinson et al., 2001, Int J Geriat Psychiatry

Memantine over Donepezil: RCT

Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil

A Randomized Controlled Trial

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Martin R. Farlow, MD
George T. Grossberg, MD
Stephen M. Graham, PhD
Scott McDonald, PhD
Ivan Gergel, MD
for the Memantine Study Group

Context Memantine is a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist. Controlled trials have demonstrated the safety and efficacy of memantine monotherapy for patients with moderate to severe Alzheimer disease (AD) but no controlled trials of memantine in patients receiving a cholinesterase inhibitor have been performed.

Objective To compare the efficacy and safety of memantine vs placebo in patients with moderate to severe AD already receiving stable treatment with donepezil.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled clinical trial of 404 patients with moderate to severe AD and Mini-Mental State Examination scores of 5 to 14, who received stable doses of donepezil, conducted at 37 US sites between June 11, 2001, and June 3, 2002. A total of 322 patients (80%) completed the trial.

Interventions Participants were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d, n=203) or placebo (n=201) for 24 weeks.

ALZHEIMER DISEASE (AD) IS A neurodegenerative disorder characterized by cognitive decline, impaired performance

Tariot et al., 2004, JAMA

Memantine over Donepezil: RCT

- Compare the efficacy and safety of m. vs. placebo in mod. To severe AD on donepezil.
- Randomized, double-blind, placebo
- Moderate to severe AD (404; 5~14/MMSE)
- Primary:
  - SIB (Severe Impairment Battery), ADCS-ADL19
- Secondary:
  - CIBIC-Plus, NPI, BRS for Geriatric Patients (selected)

Tariot et al., 2004, JAMA

Memantine over Donepezil: RCT

Table 2. Efficacy Outcomes at Week 24 (Observed Case) and at End Point (LOCF)*

Outcome Measure	Least Squares Mean Score (SE)							
	Baseline		Change From Baseline					
			End Point LOCF†			Week 24 Observed Case		
	Placebo	Memantine	Placebo	Memantine	*P* Value	Placebo	Memantine	*P* Value
SIB	80.0 (1.13)	78.0 (1.11)	–2.5 (0.69)	0.9 (0.67)	<.001	–2.4 (0.74)	1.0 (0.70)	<.001
No. of patients	197	198	196	198		153	171	
ADCS-ADL$_{19}$	35.8 (0.74)	35.5 (0.73)	–3.4 (0.51)	–2.0 (0.50)	.03	–3.3 (0.55)	–1.7 (0.51)	.02
No. of patients	197	198	197	198		152	172	
CIBIC-Plus‡	NA	NA	4.66 (0.075)	4.41 (0.074)	.03	4.64 (0.087)	4.38 (0.081)	.03
No. of patients	197	198	196	198		152	172	
NPI	13.4 (1.08)	13.4 (1.07)	3.7 (0.99)	–0.1 (0.98)	.002	2.9 (1.06)	–0.5 (0.99)	.01
No. of patients	197	198	189	193		152	171	
BGP Care Dependency Subscale	9.8 (0.46)	9.5 (0.45)	2.3 (0.38)	0.8 (0.37)	.001	2.2 (0.40)	0.6 (0.37)	.001
No. of patients	196§	198	179	185		151	172	

Abbreviations: ADCS-ADL$_{19}$, 19-item Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory; BGP, Behavioral Rating Scale for Geriatric Patients; CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input; LOCF, last observation carried forward; NA, not applicable; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery.

*SIB range of possible scores, 0 to 100; higher score indicates better function. ADCS-ADL$_{19}$ range of possible scores, 0 to 54; higher score indicates better function. CIBIC-Plus was defined as a change score, therefore baseline values are not applicable; range of possible scores, 1 (marked improvement) to 7 (marked worsening). NPI range of possible scores, 0 to 144; higher scores indicate worse symptoms. BGP range of possible scores, 0 to 70; higher scores indicate worse function.

†For the end point LOCF approach, only postbaseline assessments were carried forward.

‡Arithmetic mean.

§One patient had an incomplete BGP baseline assessment and was not included.

Primary Outcome in Major Studies

Drug	Study				1 outcome measurement																	
					Cognition			**Global**								**Function**						**BPSD**
	author	year	title	journal	ADAS-cog	MMSE	CASI	CIBIC-plus	CIBIS	CIBI	GBS	CGIC/physician	PDS	SCAG	IQCODE	DAD	SKT	ADL/time	ADCS-ADLsev	ADCS-ADL/19	SIB	BGP su
donepezil	Black, S., G.	2003	"Efficacy and tolerabilit	Stroke	O			O	O													
donepezil	Burns, A., M	1999	"The effects of donepe	Demer	O			O														
donepezil	Evans, M., A	2000	"Sustained cognitive in	Int J G	O	O																
donepezil	Greenberg, S	2000	"Donepezil therapy in	Arch N	O																	
donepezil	Pratt, R. D.	2002	"Patient populations ir	J Neur	O			O	O													
donepezil	Rogers, S. L.	1998	"A 24-week, double-bl	Neuro	O			O														
donepezil	Wilkinson, D	2003	"Donepezil in vascular	Neuro	O			O	O													
donepezil	Winblad, B.,	2001	"A 1-year, randomized	Neuro							O											
galantamine	Blesa, R., M.	2003	"Galantamine provides	Demer	O	O										O						
galantamine	Bullock, R., T	2004	"Management of patie	Demer	O																	
galantamine	Coyle, J. and	2001	"Galantamine, a cholin	Biol Ps	O																	
galantamine	Erkinjuntti, T	2003	"An open-label extens	Clin Th	O																	
galantamine	Lyketsos, C.	2004	"Long-term outcomes	Am J (	O																	
galantamine	Marcusson,	2003	"Galantamine demonst	Alzhei	O			O														
galantamine	Wilkinson, D	2001	"Galantamine: a rando	Int J G	O																	
memantine	Ditzler, K.	1991	"Efficacy and tolerabilit	Arznei										O			O	O				
memantine	Gortelmeyer,	1992	"Memantine in the tre	Arznei							O			O								
memantine	Orgogozo, J	2002	"Efficacy and safety of	Stroke	O			O														
memantine	Reisberg, B.,	2003	"Memantine in modera	N Eng				O											O			
memantine	Tariot, P. N.,	2004	"Memantine treatment	JAMA																O	O	
memantine	Winblad, B.	1999	"Memantine in severe	Int J G								O										O
rivastigmine	Farlow, M., F	2000	"A 52-week study of th	Eur Ne	O																	
rivastigmine	Kumar, V., R	2000	"An efficacy and safety	Eur J I	O			O					O									
rivastigmine	Rosler, M., R	1999	"Efficacy and safety of	BMJ 3	O			O					O									

Secondary Outcome in Major Studies

Drug	Study				2 outcome measurement																															
					Cognition					**Global**									**Function**													**Car**	**BPSD**			
	author	year	title	journal	ADAS-cog/13	MMSE	verbal recall : NYU Sto	verbal fluency	Tapping and Trace tests	CIBIC-plus	CDR-SB	GDS	CGIC	physician's global impression	DOTES/TWIS	CGIC/investigator	CGIC/caregiver	GBS	ADS	Functional Assessment Stagin	IDDD	ADFACS	patient rated QoL	Bristol ADL scale	ADL behaviour investigation	ADL/quality	ADAS-cog/13	DAD	ADCS/ADL	SIB	Functional Assessment Staging scale	Rating of carer stress	Behave-AD	NPI	BGP Care Dependency Subscale	modified D-Scale (Arnold/Ferm)
donepezil	Black, S., G.	2003	"Efficacy and tolerabilit	Stroke		O					O										O	O														
donepezil	Burns, A., M	1999	"The effects of donepe	Demer							O										O		O													
donepezil	Evans, M., A	2000	"Sustained cognitive in	Int J G																				O								O	O			
donepezil	Greenberg, S	2000	"Donepezil therapy in	Arch N			O	O									O																			
donepezil	Pratt, R. D.	2002	"Patient populations in	J Neur		O																														
donepezil	Rogers, S. L.	1998	"A 24-week, double-bl	Neuro		O					O												O													
donepezil	Wilkinson, D	2003	"Donepezil in vascular	Neuro		O					O											O														
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galantamine	Erkinjuntti, T	2003	"An open-label extens	Clin Th																								O						O		
galantamine	Lyketsos, C.	2004	"Long-term outcomes	Am J (																									O					O		
galantamine	Marcusson, J	2003	"Galantamine demonst	Alzhei																																
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memantine	Ditzler, K.	1991	"Efficacy and tolerabilit	Arznei		O			O					O												O										
memantine	Gortelmeyer,	1992	"Memantine in the tre	Arznei																					O											
memantine	Orgogozo, J	2002	"Efficacy and safety of	Stroke		O										O	O	O																		
memantine	Reisberg, B.,	2003	"Memantine in modera	N Eng		O						O								O										O	O			O		
memantine	Tariot, P. N.,	2004	"Memantine treatment	JAMA						O																								O	O	
memantine	Winblad, B. a	1999	"Memantine in severe	Int J G																																O
rivastigmine	Farlow, M., F	2000	"A 52-week study of th	Eur Ne																																
rivastigmine	Kumar, V., R	2000	"An efficacy and safety	Eur J N		O						O																								
rivastigmine	Rosler, M., R	1999	"Efficacy and safety of	BMJ 3		O						O																								

Conclusion

- Soaring R&D expenditure in CNS Drug development, and in geriatric population
- Most studies use 4 category assessments
  - Cognition
  - Global impression
  - Function
  - BPSD
  - (QOL / Burden)