

Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics

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Abstract: Donepezil is the leading compound for the treatment of Alzheimer's disease (AD) in more than 50 countries. As compared with other conventional acetylcholinesterase inhibitors (AChEIs), donepezil is a highly selective and reversible piperidine derivative with AChEI activity that exhibits the best pharmacological profile in terms of cognitive improvement, responders rate (40%–58%), dropout cases (5%–13%), and side-effects (6%–13%) in AD. Although donepezil represents a non cost-effective treatment, most studies convey that this drug can provide a modest benefit on cognition, behavior, and activities of the daily living in both moderate and severe AD, contributing to slow down disease progression and, to a lesser extent, to delay institutionalization. Patients with vascular dementia might also benefit from donepezil in a similar fashion to AD patients. Some potential effects of donepezil on the AD brain, leading to reduced cortico-hippocampal atrophy, include the following: AChE inhibition, enhancement of cholinergic neurotransmission and putative modulation of other neurotransmitter systems, protection against glutamate-induced excitotoxicity, activation of neurotrophic mechanisms, promotion of non-amyloidogenic pathways for APP processing, and indirect effects on cerebrovascular function improving brain perfusion. Recent studies demonstrate that the therapeutic response in AD is genotype-specific. Donepezil is metabolized via CYP-related enzymes, especially CYP2D6, CYP3A4, and CYP1A2. Approximately, 15%–20% of the AD population may exhibit an abnormal metabolism of AChEIs; about 50% of this population cluster would show an ultrarapid metabolism, requiring higher doses of AChEIs to reach a therapeutic threshold, whereas the other 50% of the cluster would exhibit a poor metabolism, displaying potential adverse events at low doses. In AD patients treated with a multifactorial therapy, including donepezil, the best responders are the CYP2D6-related extensive (EM)(*1/*1, *1/*10) (57.47%) and intermediate metabolizers (IM)(*1/*3, *1/*5, *1/*6, *7/*10) (25.29%), and the worst responders are the poor (PM) (*4/*4)(9.20%) and ultra-rapid metabolizers (UM) (*1xN/*1) (8.04%). Pharmacogenetic and pharmacogenomic factors may account for 75%–85% of the therapeutic response in AD patients treated with donepezil and other AChEIs metabolized via enzymes of the CYP family. The implementation of pharmacogenetic protocols can optimize AD therapeutics.

Keywords: donepezil, Alzheimer's disease, vascular dementia, CNS disorders, pharmacokinetics, pharmacodynamics, CYP2D6, pharmacogenetics

Introduction

Donepezil is the number one member of the second generation of acetylcholinesterase inhibitors (AChEIs) (ie, donepezil, rivastigmine, galantamine) (Table 1) developed for the treatment of Alzheimer's disease (AD) after the postulation in the early 1980s that AD was associated with a central cholinergic deficit (Bartus et al 1982; Whitehouse et al 1982). The first generation of AChEIs was represented by physostigmine, tacrine, velnacrine, and metrifonate of which only tacrine reached the market in 1993 with an ephemeral life due to pharmacokinetic and pharmacodynamic problems (Giacobini 2006). After the closure of tacrine production, donepezil became the mainstay of AD

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Table 1 Pharmacological properties of selected acetylcholinesterase inhibitors for the treatment of Alzheimer's disease

Properties	Tacrine	Donepezil	Rivastigmine	Galantamine
Class	Aminoacridine	Piperidine	Carbamate	Tertiary alkaloid
AChE inhibition	Reversible	Reversible	Pseudo-irreversible	Reversible
	Noncompetitive	Noncompetitive	Noncompetitive	Competitive
Dose (mg/day)	80–160	5–10	6–12	16–24
Duration	Short-acting	Short-acting	Intermediate-acting	Short-acting
Brain AChE selectivity	125	33	42,000	3,900
IC50 (nmol/L)				
Serum BuChE selectivity	7.2	988	54,000	18,600
IC50 (nmol/L)				
BuChE/AChE selectivity	0.06	30	1.3	4.8
Cmax (µg/L)	5.1 (10 mg)	7.2 (5 mg)	5.07 (2 mg × 2)	42 (12 mg × 2)
	20.7 (20 mg)	25.6 (10 mg)	14.1 (6 mg × 2)	137 (16 mg × 2)
	33.9 (30 mg)			
Tmax (h)	1–2	3–5	0.5–2	0.9–2
AUC (µg/L/h)	2–4	539	15.4 (3 mg × 2)	1.1
			55.9 (6 mg × 2)	
T1/2 (h)	1.3	50–80	0.6–2	7–8
Bioavailability (%)	17–37	100	35–40	100
Protein binding (%)	55	96	40	18
Clearance (L/h/kg)	2.42	0.13	1.5 (6 mg bid)	0.34
Vd (L/kg)	3.5–7	14	1.8–2.7	2.64
Cytochrome P450	CYP1A2	CYP2D6	Carbomoylation	CYP2D6
Metabolism	CYP2D6	CYP3A4		CYP3A4
Active metabolites	1-hydroxy-tacrine	6-O-desmethyldonepezil	NAP 226–90	Sanguinine
Urine excretion (%)	<3	17	Metabolite	50
Efficacy	4.0–5.3 vs 0.8–2.8	2.8–4.6 vs 0.7–1.2	1.9–4.9 vs 0.7–1.2	3.1–3.9 vs 1.73
ADAS-Cog vs Placebo				
Adverse effects				
Nausea	3+	3+	3+	2+
Vomiting	2+	2+	2+	2+
Diarrhea	2+	2+	2+	1+
Dizziness	2+	1+	2+	1+
Headache	1+	0	1+	0
Abdominal pain	1+	0	1+	0
Anorexia	2+	1+	1+	0
Bradycardia	0	0	0	0
Fatigue	0	1+	1+	1+
Muscle clamps	0	1+	0	0
Agitation	2+	1+	0	1+
Dyscrasia	0	0	0	0
Liver dysfunction	3+	0	0	0

Sources: Cacabelos, CIBE Database, 2005; Cacabelos 2005a, b; Bentué-Ferrer et al 2003; Giacobini 2000, 2006.

therapeutics from 1996 up to now. More than 1000 papers have been published on the properties of donepezil during the past decade (1996–2006). About 800 papers deal with donepezil in dementia (>300 clinical trials worldwide) (Table 2), and approximately 100 papers refer to the role of donepezil in other central nervous system (CNS) disorders. At the present time, donepezil is the leading compound for AD treatment in the world (marketed in 56 countries) (Sugimoto et al 2002).

Major issues for a drug to be successful include efficacy, safety, and at least some pharmacoeconomic benefit. On average, most studies with AChEIs reported by the pharma-

ceutical industry showed a cognitive enhancement of 2–3 points (vs placebo) in the ADAS-Cog score in clinical trials of 12–30 weeks' duration, with improvement in 12%–58% of patients, 5%–73% of drop-outs, and side-effects in 2%–58% of cases (Giacobini 2006). As compared with other AChEIs, donepezil exhibits the best pharmacological profile in terms of cognitive improvement (2.8–4.6 vs 0.7–1 points of difference with placebo in the ADAS-Cog scale), responders rate (40%–58%), drop-out cases (5%–13%), and side-effects (6%–13%) (Giacobini 2006). Most studies agree that donepezil is a safe drug, although important adverse drug reactions

Table 2 Selected studies with donepezil in Alzheimer's disease and vascular dementia

Author	Year	Disease	N	Study	Effect	Outcome measures	Comments
Rogers et al	1996	mAD	161	Double-blind Placebo-controlled	Positive (12 w)	ADAS-Cog; CGIC; MMSE; ADL	First reported study; 12% Dropout; No changes in ADL
Rogers et al	1998a	mAD	468	Double-blind Placebo-controlled	Positive (15 w)	ADAS-Cog; CDR-SB; CIBIC+; MMSE; QoL	35% Responders; 12% Dropout; No changes in QoL
Rogers et al	1998b	mAD	473	Double-blind Placebo-controlled	Positive (24 w) Placebo-controlled	ADAS-Cog; CDR-SB; CIBIC+; MMSE; QoL	25% Responders; 22% Dropout; No changes in QoL
Burns et al	1999	mAD	818	Double-blind Placebo-controlled	Positive (24 w)	ADAS-Cog; CDR-SB; CIBIC+; IDDD; QoL	23% Dropout; No changes in QoL
Rogers et al	2000	mAD	133	Double-blind Placebo-controlled	Positive (254 w)	ADAS-Cog; CDR-SB	Safety
Matthews et al	2000	mAD	80	Open-label	Positive (18 m)	ADAS-Cog; MMSE; NPI	Cognitive and behavioral improvements in 39% and 37% of patients, respectively
Rogers	2000	mAD		Open-label	Positive (2 y)	ADAS-Cog	Modest improvement
Greenberg et al	2000	mAD	60	Double-blind Placebo-controlled	Positive (6 w)	ADAS-Cog	
Homma et al	2000	mAD	263	Crossover Double-blind	Positive (24 w)	ADAS-Jcog; CDR-SB; CMCS; J-CGIC; MENFIS	28% Responders; 14% Dropout; 10% AEs
Winblad et al	2001	mAD	286	Double-blind Placebo-controlled	Positive (52 w)	ADL; GBS; GDS; MMSE; NPI	33% Dropout; Modest improvement
Mohs et al	2001	mAD	431	Double-blind Placebo-controlled	Positive (52 w)	ADFACS; CDR-SB; MMSE	74% Dropout; 51% Responders 38% reduction in the risk of functional decline vs placebo
Feldman et al	2001	sAD	290	Double-blind Placebo-controlled	Positive (24 w)	CIBIC+; DAD; FRS; MMSE; NPI; SIB; CGIC	Modest improvement; 16% Dropout; 83% AEs
Tariot et al	2001	m/sA DAD+CVD	208	Double-blind Placebo-controlled	Neutral (24 w)	MMSE; NPI-NH; CDR-SB; PSMS	82% completed the study; 97% AEs; concomitant medications; comorbidity; institutionalized patients; cognitive stabilization
Doody et al	2001a	AD	763	Double-blind Placebo-controlled	Positive (24 w)	MMSE; ADAS-Cog; CDR-SB	Cognitive improvement
Doody et al	2001b	mAD	205	Follow-up Placebo-controlled	Positive (1 y) Positive (6 m)	MMSE	Slower decline in MMSE scores
Parnetti et al	2002	AD	59	Placebo-controlled	Positive (6 m)	CSF AChE activity, BuChE activity; β -amyloid, tau, phosphorylated tau proteins MMSE; NPI	Decrease in AChE activity, and no changes in other biomarkers
Paleacu et al	2002	mAD	28	Open-label	Positive (6 m)		Significant improvement in behavioral symptoms
Nobili et al	2002b	mAD	25	Open-label	Positive (1 y)	SPECT (brain perfusion)	Preserved brain perfusion
Gauthier et al	2002	m/sAD	290	Placebo-controlled Randomized	Positive (24 w)	NPI	Improvement in behavioral symptoms

Continued

Table 2 Continued

Author	Year	Disease	N	Study	Effect	Outcome measures	Comments
Gauthier et al	2002a	mAD	207	Double-blind Placebo-controlled	Positive (24 w)	CIBIC+	Cognitive and functional improvement; 82% of patients showed adverse events Behavioral improvement
Gauthier et al	2002b	m/sAD	290	Double-blind Placebo-controlled	Positive (24 w)	NPI	
Wilkinson et al	2002	mAD	111	Open-label Comparative: vs rivastigmine	Positive (12 w)	ADAS-Cog	Similar improvement; less side-effects;
Krishnan et al	2003	mAD	67	Double-blind Placebo-controlled	Positive (24 w)	Cognition; MRI	Better compliance with donepezil Cognitive improvement and decrease in hippocampal atrophy
Kemp et al	2003	mAD	12	Double-blind Placebo-controlled	Positive (4 m)	ADAS-Cog; SPECT-MI muscarinic receptor binding	Cognitive improvement and increase M1 binding
Wilcock et al	2003	mAD	182	Rate-blind Comparative	Negative (52 w)	MIMSE; BrADL; ADAS-Cog; NPI; SCB	Galantamine better than donepezil
Black et al	2003	VD	603	Placebo-controlled Randomized	Positive (24 w)	ADAS-Cog; CIBIC-Plus; ADFACTS; CDR-SB	Improvement in cognition, function and ADL
Wilkinson et al	2003	VD	616	Placebo-controlled Randomized	Positive (24 w)	ADAS-Cog; CIBIC+	Improvement in cognition and global function
Feldman et al	2003	m/sAD	290	Double-blind Placebo-controlled	Positive (24 w)	DAD; IADL+; PSMS+	Slower cognitive decline and better ADL performance
Adunsky et al	2004	AD	105	Randomized Open-label	Negative	Plasma lipid profile	Increased levels of cholesterol, triglycerides, LDL and VLDL in donepezil users
Salloway et al	2004	MCI	270	Double-blind Placebo-controlled	Neutral (24 w)	NYUPDRT; ADCS CGIC-MCI; ADAS-Cog; PGA	20% dropout; 88% adverse events (73% placebo)
Holmes et al	2004	mAD	134	Randomized withdrawal	Positive (6 w)	NPI	Improvement in neuropsychiatric symptoms
Tariot et al	2004	m/sAD	404	Combination therapy: donepezil + memantine	Positive (6 m)	MMSE; ADCS-ADL; SIB; CIBIC+; NPI; BRSGP	Improved cognition, ADLs, global function, behavior and care dependence
Beusterien et al	2004	mAD	3864	Retrospective	Positive (>1 yr)	Nursing Home Placement (NHP)	4.4% vs 11.0% in controls
Seltzer et al	2004	mAD	96	Double-blind Placebo-controlled	Positive (24 w)	ADAS-Cog; MMSE; CMBT; CDR-SB; PGAS; AS	Early-stage AD
Courtney et al AD2000 Collaborative Group 2004	2004	mAD	565	Double-blind Double randomization	Negative (12 w)	Entry to institutional care Progression of disability/BADLS	Not cost-effective; No effect on institutionalization rate; No effect on progression of disability
Jones et al	2004	mAD	64	Open-label Comparative: donepezil vs galantamine	Positive (12 w)	ADAS-Cog; MMSE; DAD Satisfaction rate	Donepezil superior to galantamine

Continued

Table 2 Continued

Author	Year	Disease	N	Study	Effect	Outcome measures	Comments
Finkel et al	2004	mAD	120	Placebo-controlled Randomized	Neutral (12 w)	NPI; CGI; CGI-S	Neutral effect of the combination therapy
Thomas et al	2005	VD/AD	16/15	Open-label	Positive (16 w)	MMSE; working memory tests; delayed recognition memory	Marginal effects on MMSE score Gains in working memory
Bartorelli et al	2005	mAD	225	Observational Switching from donepezil to rivastigmine	Positive (3 m)	MMSE; ADL; IADL; CGIC	Improvement in cognitive function after switching (>60% responders)
Hashimoto et al	2005	mAD	54	Open-label	Positive (1 yr)	MRI; Mean annual rate of hippocampal volume loss	Control subjects have never been under AChE treatment
Klinger et al	2005	mAD	913	Post-Marketing Surveillance	Positive (3 m)	MMSE; QoL	Observational PMS study in patients previously treated with memantine or nootropics
Bullock et al	2005	m/sAD	994	Double-blind Comparative	Neutral	Cognitive function; activities of daily living; global functioning; behavioral symptoms	Comparative study: donepezil vs rivastigmine; Better results with rivastigmine in carriers of the wild-type BuChE genotype
Bizzarro et al	2005	mAD	41	Observational	Negative (1 yr)	MMSE; APOE	No cognitive improvement; APOE-related responses
Roman et al	2005	VD	1219	Double-blind Placebo-controlled	Positive (24 w)	ADAS-Cog; MMSE; CIBIC+; CDR-SB; ADFACTS; ADFACTS-IADL	Combined analysis of 2 large-scale trials in 109 investigational sites in USA, Europe, Canada, and Australia
Petersen et al	2005	MCI	769	Double-blind	Negative (3 yrs)	Conversion to AD; cognition; function	Comparative with vitamin E; Positive results in APOE-4 carriers
Ancoli- Israel et al	2005	mAD Sleep disorder	63	Double-blind Placebo-controlled	Positive (1 yr) Neutral (8 w)	Actigraphy	No effect on sleep; Comparative: donepezil vs galantamine
Feldman et al	2005	m/sAD	290	Placebo-controlled Subgroup analysis	Positive	CIBIC+; MMSE; SIB; NPI; DAD	Benefits over placebo on global, cognitive, functional, and behavioral measures
Winblad et al	2006a	sAD	128	Double-blind, parallel-group, Placebo-controlled	Positive (6 m)	Severe Impairment Battery (SIB) Modified Alzheimer's Disease Cooperative Study activities of daily living inventory for sAD (ADCS-ADL-severe)	Nursing home patients
Johannsen et al	2006	mAD	619	Open-label 12-24 w Double-blind Placebo-controlled Single-blind 12 w	Positive (12-24 w)	ADAS; MMSE; DAD; NPI	69% Responders; 31% Non-responders; Cognitive and behavioral benefit
Bullock et al	2006	mAD	994	Randomized	Partial effects (2 yrs)	SIB; NPI; GDS; MMSE; ADCS-ADL	Age-dependent response; BuChE genotype-related response
Paci et al	2006	VD	10	Open-label	Positive (1 m)	Cognition; P300 ERP	Improvement in P300 latency
Winblad et al	2006b	m/sAD	286	Open-label	Positive (3 yrs)	MMSE; GBSS; GDS; NPI	Delayed progression of disease; 90% ADRs

Continued

Table 2 Continued

Author	Year	Disease	N	Study	Effect	Outcome measures	Comments
Shimizu et al	2006	mAD	51	Open-label	Neutral (10-14 m)	MMSE; SPECT (r-CBF)	Improvement in frontal rCBF
Touchon et al	2006	AD-DLB	94	Retrospective vs rivastigmine	Negative (2 yrs)	MMSE; SIB; GDS; NPI; ADCS-ADL; ITT-LOCF	Rivastigmine superior to donepezil in AD with DLB-like symptoms
Van Dyck et al	2006	m/sAD	404	Combination therapy with memantine	Neutral (24 w)	ADCS-ADL; SIB; CIBIC+; NPI	Improvement and stabilization of symptoms

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-Jcog, Alzheimer's Disease Assessment Scale-Cognitive subscale, Japanese version; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADCS CGIC-MCI, Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change for MCI; ADFACS-AD, Functional Assessment and Change Scale; ADFACS-IADL, Instrumental activities of daily living; ADL, Activities of Daily Living; AS, Apathy Scale; BADLS, Bristol activities of daily living scale; BRSGP, Behavioral Rating Scale for Geriatric Patients; 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; CMBT, Computerized Memory Battery Test; CMCS, Caregiver-rated Modified Crichton Scale; DAD, Disability Assessment for Dementia; DLB, Dementia with Lewy bodies; FRS, Functional Rating Scale; GBSS, Gottfrids-Brane-Stein scale; GDS, Global Deterioration Scale; IDDD, Modified Interview for Deterioration in Daily Living in Dementia; IADL+, modified instrumental activities of daily living scale; ITT-LOCF, Intention-to-treat last observation carried forward; J-CGIC, Japanese version of CGIC; mAD, mild-moderate Alzheimer's disease; CI, mild cognitive impairment; MENFIS, Mental Function Impairment Scale; MMSE, Mini-Mental Status Examination; PI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home Version; NYUPDRT, New York University Paraglyph Delayed Recall test; QoL, Quality of Life; PGAS, Patient Global Assessment Scale; PSMSt+, Modified Physical Self Maintenance Scale; PSP, progressive supranuclear palsy; sAD, moderate-severe Alzheimer's disease; SD, senile dementia; SIB, Severe Impairment Battery; VD, vascular dementia.

(ADRs) have been reported in the international literature (Table 3). However, when evaluating efficacy and safety issues with AChEIs in AD, methodological limitations in some studies reduce the confidence of independent evaluators in the validity of the conclusions drawn in published reports (Clegg et al 2001; Lanctôt et al 2003; Hogan et al 2004; Kaduszkiewicz et al 2005; Loveman et al 2006). For pharmacoeconomic aspects, some studies assessing the cost-effectiveness of ChEIs suggest that AChEI therapy provides benefit at every stage of disease, with better outcomes resulting from persistent, uninterrupted treatment (Fillit 2000; Sano 2004; Feldman et al 2004), whereas other studies indicate that AChEIs are not cost-effective, with benefits below minimally relevant thresholds or cost-neutral (Clegg et al 2001; Wimo 2004; Wimo et al 2004; Loveman et al 2006). The average annual cost per person with dementia ranges from US\$15,000 to US\$50,000, depending upon disease stage and country, with a lifetime cost per patient of more than US\$175,000. Approximately, 80% of the global costs of dementia (direct and indirect costs) are assumed by the patients and/or their families, and 10%–20% of the costs of dementia are attributed to pharmacological treatment (Cacabelos 2005a, 2005b). Considering an average survival time (from diagnosis to death) of 10 years in optimal conditions, receiving 4–6 different drugs/day, a patient with dementia expends about US\$4500–6000 per year (≈US\$50,000 in a decade) in medicines.

Since the past experience in AD therapeutics was regrettably unsuccessful, donepezil is a good paradigm to interpret the past and to plan ahead future pharmacological challenges in order to optimize the treatment of dementia, incorporating novel data about the impact of pharmacogenetics on AD therapeutics and the influence of genetic factors on efficacy and safety issues.

Molecular pathology of Alzheimer's disease

AD is a polygenic/multifactorial complex disorder characterized by the premature death of neurons. More than 200 different genes distributed across the human genome have been potentially involved in the pathogenesis of AD (Cacabelos et al 2005). The genetic defects identified in AD during the past 25 years can be classified into 3 main categories: (a) Mendelian or mutational defects in genes directly linked to AD, including (i) 18 mutations in the amyloid beta (A β) precursor protein (APP) gene (21q21); (ii) 142 mutations in the presenilin 1 (PS1) gene (14q24.3); and (iii) 10 mutations in the presenilin 2 (PS2) gene (1q31-q42). (b) Multiple polymorphic variants of

Table 3 Adverse drug reactions reported in clinical trials with donepezil in Alzheimer's disease and other CNS disorders

ADRs	Frequency ^a	Disease
Pain	15%	mAD
Common cold	9%	mAD
Headache	8%	mAD
Fatigue	5%	mAD
Hypertension	5%	mAD
Urinary tract infections	7%–17%	mAD, sAD
Abdominal disturbance	6%	mAD
Stomach upset	6%	mAD
Anorexia	6%	mAD
Bloating	5%	mAD
Hematic and lymphatic disorders	5%	mAD
Metabolic and nutritional disorders	6%	mAD
Musculoskeletal problems	17%–25%	mAD, sAD, DS, DLB
Accidental fall	11%–13%	mAD, sAD
Anxiety	6%–7%	mAD, sAD
Agitation	24%–56%	mAD, sAD, DS
Insomnia	11%	mAD
Confusion	8%	mAD
Depression	8%	mAD
Dizziness	7%	mAD
Restlessness	5%	mAD
Vertigo	5%	mAD
Accidental injury	6%–11%	mAD, sAD
Gastroenteritis	6%	sAD
Weight loss	15%–20%	mAD, sAD
Diarrhea	9%	mAD, sAD
Coughing	5%	mAD
Nasal congestion	5%	mAD
Pneumonia	9%–10%	sAD
Cystitis	6%	sAD
Nausea	6%–8%	mAD, sAD
Asthenia	3%–5%	mAD, sAD
Accidental bone fracture	6%–8%	mAD, sAD
Constipation	4%	sAD
Skin problems	14%	mAD, sAD, DLB
Hallucinations	5%–6%	mAD, sAD
Somatosensory alterations	5%	mAD
Urogenital disturbances	24%	mAD
Unusual/abnormal dreams/nightmares	10%–34.3%	mAD, MCI, MS
Cardiovascular dysfunction	30%–40%	mAD, sAD
Lipid metabolism alterations	20%–35%	mAD
Syncope	1%–10%	sAD
Tardive dyskinesia	1%–4%	mAD, SCZ, PSYD
Catatonia	<1%	DLB
Pisa syndrome	<1%	mAD, sAD, PD
Athetosis	<1%	m/sAD
Parkinsonism	<1%	DLB
Neuroleptic malignant syndrome	<1%	mAD, SCZ
Delirium	1%–2%	m/sAD
Extrapyramidal symptoms	1%–5%	PD; SCZ
Toxic hepatitis	<1%	AD
Dyskinetic disorders	<1%	AD
Syncope	<1%	AD
Pancreatitis	<1%	AD
Seizures	1%–3%	AD
Purpuric rash	<1%	AD
Prolonged effects of anesthesia	<1%	AD

^aEstimated values from clinical trials and clinical observations reported in the international literature (n = 112)

Abbreviations: DLB, dementia with Lewy bodies; DS, Down's syndrome; mAD, Mild-moderate Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease; PSYD; psychotic disorders; sAD, moderate–severe Alzheimer's disease; SCZ, schizophrenia.

risk characterized in more than 200 different genes distributed across the human genome can increase neuronal vulnerability to premature death (Cacabelos et al 2005). Among these genes of susceptibility, the apolipoprotein E (APOE) gene (19q13.2) is the most prevalent as a risk factor for AD, especially in those subjects harbouring the APOE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia. APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD. (c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity. It is also likely that defective functions of genes associated with longevity may influence premature neuronal survival, since neurons are potential pacemakers defining life span in mammals. All these factors may interact in as yet unknown genetic networks leading to a cascade of pathogenic events characterized by abnormal protein processing and misfolding with subsequent accumulation of abnormal proteins (conformational changes), ubiquitin-proteasome system dysfunction, excitotoxic reactions, oxidative and nitrosative stress, mitochondrial injury, synaptic failure, altered metal homeostasis, dysfunction of axonal and dendritic transport and chaperone misoperation (Bossy-Wetzel et al 2004; Cacabelos 2005a, b; Cacabelos et al 2005). Some of these mechanisms are common to several neurodegenerative disorders which differ depending upon the gene(s) affected and the involvement of specific genetic networks, together with cerebrovascular factors, epigenetic factors, oxidative stress phenomena, and environmental conditions (eg, nutrition, toxicity, social factors) (Bossy-Wetzel et al 2004; Cacabelos et al 2005; Mattson and Magnus 2006). The higher the number of defective genes involved in AD pathogenesis, the earlier the onset of the disease, the faster its clinical course and the poorer its therapeutic outcome (Cacabelos 2005a, b; Cacabelos et al 2005).

Although the amyloid hypothesis is recognized as the *primum movens* of AD pathogenesis (Selkoe and Podlisny 2002; Suh and Checler 2002; Cacabelos et al 2005), mutational genetics associated with amyloid precursor protein (APP) and presenilin (PS) genes alone (<10% of AD cases) does not explain in full the neuropathologic findings present in AD, represented by amyloid deposition in senile plaques and vessels (amyloid angiopathy), neurofibrillary tangle (NFT) formation due to hyperphosphorylation of tau protein, synaptic and dendritic desarborization and neuronal loss (Goedert and Spillantini 2006). These findings are accompanied by neuroinflammatory reactions, oxidative stress, and free radical formation probably associated with mitochondrial

dysfunction, excitotoxic reactions, alterations in cholesterol metabolism and lipid rafts, deficiencies in neurotransmitters (especially acetylcholine) and neurotrophic factor function, defective activity of the ubiquitin-proteasome, and chaperone systems and cerebrovascular dysregulation (Cacabelos et al 2005). All these neurochemical events are potential targets for treatment; however, it is very unlikely that a single drug be able alone to neutralize the complex mechanisms involved in neurodegeneration (Cacabelos 2005a, b; Cacabelos et al 2005; Cacabelos and Takeda 2006).

The cholinergic hypothesis

Before the understanding of the complex pathology of AD, in the late 1970s and early 1980s it was believed that AD-related memory dysfunction was in part due to a cholinergic deficit in the brain of affected people due to a loss of neurons in the basal forebrain, this giving rise to the cholinergic hypothesis of AD (Bartus et al 1982; Whitehouse et al 1982; Francis et al 1999). The role of acetylcholine on memory function had been postulated many years before, and it was reasonable to think that a cholinergic deficit associated with an age-related decline in the number of neurons (50%–87%) of the nucleus basalis of Meynert accompanied by a reduced number of cholinergic synapses in cortical fronto-parietal-temporal regions and in the entorhinal cortex, might justify the memory deficit present in AD patients (Bartus et al 1982). From the 1950s to the 1980s “the amyloid hypothesis” and “the tau hypothesis” were elaborated, and both theories became the dominant and confronted pathogenic mechanisms potentially underlying AD-related neurodegeneration (Goedert and Spillantini 2006). However, recent genomic studies suggest that amyloid deposition in senile plaques, NFT and cholinergic deficits are but the phenotypic expression of the disease, and that the causative mechanism of premature neuronal death should be upstream of all these pathogenic events (Cacabelos et al 2005).

Since choline donors (precursors) and acetylcholine itself were substances of difficult pharmacological management (or useless to increase brain cholinergic neurotransmission), and, paradoxically, considering that acetylcholinesterase activity progressively decreased in AD brains in parallel with cognitive deterioration, AChEIs were proposed as an option to inhibit acetylcholine degradation in the synaptic cleft and to increase choline reuptake at the presynaptic level with the aim of enhancing acetylcholine synthesis in presynaptic terminals, this facilitating cholinergic neurotransmission (Giacobini 2006). The first candidate to fulfil this criteria was tacrine (tetrahydroaminoacridine) (Summers et al 1986),

which after its introduction in the market in 1993 soon fell out of favor due to its hepatotoxicity and poor tolerability; 3 years later, in 1996, donepezil was approved by the FDA for the treatment of mild-to-moderate cases of AD. The other AChEIs, rivastigmine and galantamine, were introduced several years later (Giacobini 2006).

Pharmacological properties of donepezil

Donepezil, 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine hydrochloride (E2020), is an indanone benzylpiperidine derivative (Sugimoto et al 1995) with selective reversible AChEI activity in the CNS and other tissues (Nochi et al 1995; Giacobini et al 1996; Sugimoto et al 2002). Donepezil is approximately 10 times more potent than tacrine as an inhibitor of acetylcholinesterase (AChE), and 500–1000-fold more selective for AChE over butyrylcholinesterase (BuChE). This compound is slowly absorbed from the gastrointestinal tract and has a terminal elimination half-life of 50–70 hours in young volunteers (>100 hours in elderly subjects) (Ohnishi et al 1993). After extensive metabolism in the liver, the parent compound is 93% bound to plasma proteins (Heydorn 1997).

AChEIs exhibit different affinities and selectivity for AChE and BuChE; however, most of them display a similar potency and clinical efficacy at conventional doses, this fact suggesting that these compounds may exert their therapeutic effects via collateral mechanisms unrelated to or indirectly linked with cholinesterase inhibition. Their chemical structures are also responsible for their pharmacokinetic and pharmacodynamic properties (Nordberg and Svensson 1999). For instance, physostigmine and rivastigmine are carbamates with pseudo-irreversible AChE-BuChE inhibition; tacrine is an acridine with reversible inhibition on the AChE-BuChE substrates; metrifonate is an organophosphate with irreversible inhibition of AChE-BuChE; donepezil is a piperidine with highly specific, reversible AChE inhibition; galantamine is a phenanthrene with reversible inhibition of AChE-BChE; and huperzine A is a pyridine with specific, reversible AChE inhibition (Giacobini 2006) (Table 1). The order of inhibitory potency (IC₅₀) towards AChE activity under optimal assay conditions for each AChEI is the following: physostigmine (0.67 nM) > rivastigmine (4.4 nM) > donepezil (6.7 nM) > TAK-147 (12 nM) > tacrine (77 nM) > ipidacrine (270 nM). According to this study performed by Eisai scientists, the benzylpiperidine derivatives donepezil and TAK-147 showed high selectivity for AChE over BuChE; the carbamate deriva-

tives showed moderate selectivity, while the 4-aminopyridine derivatives tacrine and ipidacrine showed no selectivity (Ogura et al 2000). More recent studies indicate that donepezil is 40–500-fold more potent than galantamine in inhibiting AChE. Clearance of galantamine from the brain is faster than donepezil. Ki values of brain AChE inhibition for galantamine and donepezil, respectively, are 7.1–19.1 and 0.65–2.3 µg/g in different species, suggesting that for a similar degree of brain AChE inhibition, 3–15 times higher galantamine than donepezil doses are needed (Geerts et al 2005).

The pharmacokinetic properties of AChEIs are also different. Tacrine, donepezil, and galantamine are metabolized in the liver via the cytochrome P450 system (CYP1A2-, CYP2D6-, CYP3A4-related enzymes), whereas rivastigmine is metabolized through carbomoylation (Table 1). Donepezil potentially may interact with drugs metabolized via CYP1A2-, CYP2D6-, and CYP3A4-related enzymes; however, formal pharmacokinetic studies have revealed no clinically meaningful interactions with memantine, risperidone, sertraline, carbidopa/levodopa, theophylline, furosemide, cimetidine, warfarin, and digoxin (Tiseo et al 1998a, b, c, d, e, f; Seltzer 2005). Their half-life also differ from 2–4 hours (tacrine, metrifonate, phenserine) to 4–6 hours (rivastigmine, galantamine), and 73 hours (donepezil). Bioavailability is maximum for galantamine (100%) and metrifonate (90%), both substances showing the lowest plasma protein binding (10–20%) in contrast to donepezil (96%) (Nordberg and Svensson 1999; Farlow 2001; Bentué-Ferrer et al 2003; Farmow 2003; Giacobini 2006). In animals, donepezil is found unchanged in brain, and no metabolites are detected in the nervous tissue. In plasma, urine, and bile, most donepezil metabolites are O-glucuronides (Matsui et al 1999). In healthy volunteers, donepezil is hepatically metabolized and the predominant route for the elimination of both parent drug and its metabolites is renal, as 79% of the recovered dose was found in the urine with the remaining 21% found in feces. Moreover, the parent compound is the predominant elimination product in urine. The major metabolites of donepezil include M1 and M2 (via O-dealkylation and hydroxylation), M11 and M12 (via glucuronidation of M1 and M2, respectively), M4 (via hydrolysis) and M6 (via N-oxidation) (Tiseo et al 1998f).

After 14 days administration of donepezil, the cerebral acetylcholine level is increased by 35% and the AChE activity is decreased by 66% and 32% in rat brain and blood, respectively. No changes are detected in choline acetyltransferase activity, or the levels of vesicular acetylcholine transporter, choline transporter, or muscarinic receptors. The expression of various cholinergic genes is not affected by donepezil. Donepezil increases acetylcholine concentration in the

synaptic cleft of the hippocampus mostly through AChE inhibition (Kosasa et al 1999) and produces a dose-dependent increase in hippocampal theta rhythm amplitude elicited by stimulation of the brainstem reticular formation (Kinney et al 1999). AChE activity in human blood shows 60%–97% and 43%–89% of pre-exposed level after 1 and 3 days of donepezil administration at a daily dose of 5 mg, respectively (Haug et al 2005). The current doses of donepezil at the clinical setting are 5 and 10 mg/day. Above 10 mg, AChE inhibition is assumed to reach a plateau (Jann et al 2002).

It is likely that the modest (and variable) therapeutic effects of AChEIs are related to their pharmacological properties and individual capacity to inhibit AChE activity in AD brains. Rakonczay (2003) compared the effects of 8 AChEIs on AChE and BuChE activity in normal human brain cortex. The most selective AChEIs, in decreasing order were: TAK-147, donepezil, and galantamine. For BuChE, the most specific was rivastigmine; however, none of these AChEIs was absolutely specific for AChE or BuChE. Among these inhibitors, tacrine, bis-tacrine, TAK-147, metrifonate, and galantamine inhibited both the G1 and G4 AChE forms equally well (Rakonczay 2003).

The cognitive effects of AChEIs have been studied under different paradigms. The most frequent experiments have been performed in animals with cholinergic deficits or with lesions of the nucleus basalis of Meynert, as well as in animal models of AD and transgenic animals.

Donepezil can also act on targets other than cholinesterases in the brain. Among possible indirect actions of AChEIs to protect AD neurons, several options have been postulated. In dissociated hippocampal neurons, donepezil reversibly inhibits voltage-activated Na⁺ currents, and delays rectifier K⁺ current and fast transient K⁺ current. The inhibition of donepezil on rectifier K⁺ currents is voltage-dependent, whereas that on fast transient currents is voltage-independent. The blocking effects of donepezil on the voltage-gated ion channels are unlikely to contribute to its clinical effects in AD (Yu and Hu 2005).

Donepezil up-regulates nicotinic receptors in cortical neurons, this probably contributing to enhance neuroprotection (Kume et al 2005). It has also been suggested that AChEIs might promote non-amyloidogenic pathways of APP processing by stimulation of α -secretase mediated through protein kinase C (PKC) (Pakaski et al 2001). In the transgenic Tg2576 mouse model of AD, which exhibits age-dependent β -amyloid deposition in the brain as well as abnormalities in the sleep-wakefulness cycle probably due to a cholinergic deficit, the wake-promoting efficacy of

donepezil is lower in plaque-bearing Tg2576 mice than in controls (Wisor et al 2005). In AD cases, donepezil increases the percentage of REM (rapid eye movements) sleep to total sleep time, improving sleep efficiency and shortening sleep latency (Mizuno et al 2004; Moraes et al 2006). In healthy volunteers, donepezil specifically enhances the duration of REM sleep (% sleep period time) and the number of REMs (Nissen et al 2005). The activation of the visual association cortex during REM sleep by donepezil might be responsible for the development of abnormal dreams and nightmares in AD (Singer et al 2005).

The influence of AChEIs on APP processing and inhibition of β -amyloid formation, at least in the case of some AChEIs (eg, phenserine), does not appear to be associated with cholinesterase inhibition but with a novel mechanism regulating translation of APP mRNA by a putative interleukin-1 or TGF- β responsive element which has been proposed as a target for drug development (Shaw et al 2001). Donepezil and other AChE noncovalent inhibitors are able to inhibit AChE-induced β -amyloid aggregation (Tumiatti et al 2004). AChEIs may also protect against vascular damage and amyloid angiopathy. In mild–moderate AD patients, increased levels of markers of endothelial dysfunction, such as thrombomodulin and sE-selectin have been observed. After treatment with AChEIs for 1 month, the levels of both parameters are markedly reduced, with values approaching normal ranges (Borroni et al 2005). In the Tg2576-transgenic mouse model in which, at 9–10 months of age, Tg⁺ mice develop amyloid plaques and impairments on paradigms related to learning and memory as compared to transgene-negative (Tg⁻) mice, physostigmine and donepezil improve deficits in contextual and cued memory in Tg⁺, but neither drug alter the deposition of amyloid plaques (Dong et al 2005). In contrast, donepezil protects against the neurotoxic effects induced by β -amyloid(1-40) in primary cultures of rat septal neurons (Kimura et al 2005). In another transgenic model of AD, the AD11 anti-nerve growth factor (anti-NGF) mice, oral administration of ganstigmine (CHF2819) and donepezil reverses the cholinergic and behavioral deficit in AD11 mice but not the amyloid and phosphotau accumulation, uncovering different mechanisms leading to neurodegeneration in AD11 mice (Capsoni et al 2004).

Probably via cholinergic modulation at the hypothalamic level, donepezil is able to reverse the age-related down-regulation of the GH/IGF-1 axis in elderly males in basal conditions and after GHRH stimulation. GHRH-induced GH response is magnified by more than 50% after treatment with donepezil in healthy elderly subjects (Obermayr et al 2005). The

enhancement of the somatotropinergic system (GRF-GH-IGF axis) associated with donepezil treatment might contribute to activate GRF/GH-related neurotrophic mechanisms (Cacabelos et al 1988a, b). AChEIs also influence pro-inflammatory cytokines released from peripheral blood mononuclear cells, increasing oncostatin M, IL-1 β , and IL-6 levels in AD patients after treatment (Reale et al 2005).

Glutamate-related excitotoxicity is an additional deleterious mechanism secondarily contributing to AD neuropathology (Cacabelos et al 1999). The neuroprotective properties of AChEIs on glutamate-induced excitotoxicity were investigated in primary cultured cerebellar granule neurons. Exposure of neurons to glutamate results in neuronal apoptosis. In this model, bis(7)-tacrine, a novel dimeric AChEI markedly reduces glutamate-induced apoptosis in a time- and dose-dependent manner; however, donepezil and other conventional AChEIs do not show any effect (Li et al 2005). Donepezil blocks the responses of recombinant NMDA receptors expressed in *Xenopus oocytes*. The blockade is voltage-dependent, suggesting a channel blocker mechanism of action which is not competitive at either the L-glutamate or glycine binding sites. The low potency of donepezil indicates that NMDA receptor blockade does not contribute to its therapeutic effect in AD; however, donepezil binds to the sigma1 receptor with high affinity and shows antidepressant-like activity in the mouse forced-swimming test as does the sigma1 receptor agonist igmesine. All AChEIs attenuate dizocilpine-induced learning impairments, but only the donepezil and igmesine effects are blocked by BD1047 or the antisense treatment, suggesting that donepezil behaves as an effective sigma1 receptor agonist and that interaction with sigma1 protein, but not NMDA receptor, might be involved in the pharmacological activity of donepezil (Maurice et al 2006). Other studies indicate that donepezil has a neuroprotective effect against oxygen-glucose deprivation injury and glutamate toxicity in cultured cortical neurons, and that this neuroprotection may be partially mediated by inhibition of the increase of intracellular calcium concentration (Akasofu et al 2006).

Donepezil influences cells viability and proliferation events in SH-SY5Y human neuroblastoma cells. Short- and long-exposure of these cells to donepezil induced a concentration-dependent inhibition of cell proliferation unrelated to muscarinic or nicotinic receptor blockade or apoptosis. Donepezil reduces the number of cells in the S-G2/M phases of the cell cycle, increases the G0/G1 population, and reduces the expression of two cyclins of the G1/S and G2/M transitions, cyclin E and cyclin B, in parallel with an increase in the expression of the cell cycle inhibitor p21

(Sortino et al 2004). Using the same in vitro model, others have reported that galantamine, donepezil, and rivastigmine afford neuroprotection through a mechanism that is likely unrelated to AChE inhibition, suggesting that at least donepezil and galantamine, but not rivastigmine, may exert their potential neuroprotective effects via α 7 nicotinic receptors and the PI3K-Akt pathway (Arias et al 2005). In addition, donepezil increases action potential-dependent dopamine release (Zhang et al 2004) and modulates nicotinic receptors of substantia nigra dopaminergic neurons (Di Angelantonio et al 2004).

Donepezil in Alzheimer's disease

Most clinical trials with donepezil in AD during the past 10 years have been performed in patients with mild-to-moderate dementia (mAD) (Rogers et al 1996, 1998a, 1998b; Burns et al 1999; Homma et al 2000; Doody et al 2001a, b; Mohs et al 2001; Winblad et al 2001) (Table 2), and a small number of studies have been carried out in severe cases of AD (sAD) (Feldman et al 2001; Bullock et al 2005; Winblad et al 2006a) (Table 2). More than 10,000 patients recruited from 26 different countries have been included in major clinical trials with AChEIs (24–30 weeks' duration) during the past decade (Giacobini 2006). The typical outcome measures in most trials include psychometric assessment, behavior and function with different scales. Although the differences in the design of clinical trials is obvious, in patients treated with donepezil the differences with placebo range from 0.7–1.2 to 2.8–4.6 points in the ADAS-Cog (Giacobini 2006; Whitehead et al 2004). Despite this optimistic view resulting from the observation of selected trials (Table 2), many other studies and meta-analyses (Glegg et al 2001; Lanctôt et al 2003; Kaduszkiewicz et al 2005; Loveman et al 2006; Birks 2006; Birks et al 2006) indicate that AChEIs in general and donepezil in particular are of poor efficacy in AD. In 16 trials with 5159 treated patients (placebo = 2795 patients) the pooled mean proportion of global responders to AChEIs in excess of that of placebo was 9%. The rate of adverse events, dropout for any reason and dropout because of adverse events were also higher among patients receiving AChEIs than among those receiving placebo, with an excess proportion of 7%–8% (Lanctôt et al 2003). In this meta-analysis, including 8 trials with donepezil, 2 trials with rivastigmine and 5 trials with galantamine, the cognitive response was positive in 23%–35% of patients treated with donepezil, in 30% of patients treated with rivastigmine, and in 20–32% of patients treated with galantamine. The dropout rate was 20%–60% due to adverse events (Lanctôt et al 2003).

In a meta-analysis including 22 trials published from 1989 to 2004, 12 of 14 studies showed an improvement of 1.5–3.9 points in the ADAS-Cog; however, because of flawed methods and small clinical benefits, the German evaluators established that the scientific basis for recommendations of AChEIs in AD was questionable (Kaduszkiewicz et al 2005). In a 10-study meta-analysis of donepezil in AD and two-study combined analysis of donepezil in vascular dementia (VD), an Irish group concluded that although there are differences between AD and VD patients in comorbid conditions and concomitant medications, donepezil is effective and well tolerated in both types of dementia (Passmore et al 2005). In the AD2000 clinical trial of Courtney et al (2004), no significant benefits were seen with donepezil compared with placebo in institutionalization or progression of disability. Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil (Courtney et al 2004). In a critical appraisal of the AD2000 study, the first long-term RCT not sponsored by the pharmaceutical industry, a German group led by Kaiser et al (2005) concluded that the widespread use of AChEIs in AD is not supported by current evidence, and that long-term-randomized controlled trials focusing on patient-relevant outcomes instead of cognitive scores are urgently needed (Kaiser et al 2005).

Recent studies in early-stage AD suggest significant treatment benefits of donepezil, supporting the initiation of therapy early in the disease course to improve daily cognitive functioning (Seltzer et al 2004). During the past decade more than 100 papers dealt with the use of AChEIs or memantine in severe AD (sAD), but only a few studies provide evidence in favor of a positive therapeutic intervention with donepezil in sAD (Feldman et al 2001, 2003, 2005; Bullock et al 2005; Forchetti 2005; Winblad et al 2006a). In the international literature there are 13 articles related to donepezil in sAD, but only 3 fulfil strict criteria for further consideration (Rawls 2005)

In one study, to evaluate efficacy and safety of donepezil in sAD, Feldman et al (2001) found that donepezil had significant benefits over placebo on global, cognitive, functional, and behavioral measures in patients with sAD (Feldman et al 2001, 2005). In another study of Feldman et al (2003), donepezil demonstrated a significantly slower decline than placebo in instrumental and basic ADLs in patients with m/sAD. Bullock et al (2005) found similar effects of donepezil and rivastigmine on cognition and behavior in m/sAD. Winblad et al (2006a) have studied 248 patients with severe

AD (sAD) (MMSE score: 1–10) living in nursing homes of Sweden for 6 months. The patients ($n = 128$) received 5 mg/day of donepezil for 30 days and then 10 mg/day thereafter. The primary end points in this study were change from baseline to month 6 in the severe impairment battery (SIB) and modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe AD (ADCS-AD-severe). Under this protocol, 95 patients assigned donepezil and 99 patients assigned placebo ($n = 120$) completed the study. AD patients treated with donepezil improved more in SIB scores and declined less in ADCS-ADL-severe scores after 6 months of treatment compared with baseline than did the patients enrolled in the placebo group (Winblad et al 2006a).

To evaluate the representation of frail older adults in randomized controlled trials (RCTs), and to assess consequences of under representation by analyzing drug discontinuation rates, Gill et al (2004) studied a cohort of older adults newly dispensed donepezil ($n = 6424$) in Ontario between September 2001 and March 2002, and compared patients dispensed donepezil to clinical trials subjects. In this interesting study, between 51% and 78% of the Ontario cohort would have been ineligible for RCT enrolment. Patients dispensed donepezil were older (>80 years) and more likely to be in long-term care than RCT subjects. Overall, 27.8% of the Ontario cohort discontinued donepezil within 7 months of initial prescription, and the discontinuation rates were significantly higher for patients with a history of obstructive lung disease, active cardiovascular disease, or parkinsonism (Gill et al 2004).

It would be highly recommendable that outcome measures of efficacy in the long-term incorporate specific AD-related biomarkers (eg, serum markers, cerebro-spinal fluid [CSF] markers, neuroimaging biomarkers [MRI, fMRI, PET, SPECT], brain atrophy rate, brain perfusion, optical topography) (McMahon et al 2000; Jagust 2004; Dickerson and Sperling 2005). In this regard, PET studies have demonstrated that donepezil-induced inhibition of cortical AChE is modest (19%–24%) in patients with mAD. In the brain of AD patients assessed with an AChE tracer by PET scanning, treatment with donepezil for 3 months reduced AChE activity by 39% in the frontal cortex, 29% in the temporal cortex, and 28% in the parietal cortex (Kaasinen et al 2002). The degree of cortical AChE inhibition correlates with changes in executive and attentional functions (Bohnen et al 2005). Long-term treatment with donepezil can lead to a lesser deterioration in qEEG, paralleling a milder neuropsychological decline (Rodríguez et al 2002), with reduction of slow-wave activity in frontal and temporo-parietal areas (Kogan et al 2001). Mean P300 ERPs are also improved in dementia

after donepezil treatment (Werber et al 2001). By using the rate of hippocampal atrophy as a surrogate marker of disease progression, Hashimoto et al (2005) found that treatment with donepezil slows the progression of hippocampal atrophy in AD (mean annual rate of hippocampal volume loss: 3.82%) as compared with untreated patients (5.04%). Smaller hippocampal volume and inward variation of the lateral and inferomedial portions of the hippocampal surface were correlated with a poorer response to donepezil therapy in dementia (Csernansky et al 2005). AD patients who show more severe cholinergic dysfunction and less severe structural damage of the hippocampus and parahippocampus are likely to respond to donepezil treatment (Tanaka et al 2003a). Atrophy of the substantia innominata was more pronounced in transiently and continuously responding groups than in non-responders. Logistic regression analysis revealed that the overall discrimination rate with the thickness of the substantia innominata was 70% between responders and non-responders, suggesting that atrophy of the substantia innominata on MRI helps to predict response to donepezil treatment in AD (Tanaka et al 2003b). Krishnan et al (2003) have found that donepezil treated patients had significantly smaller mean decreases in total and right hippocampal volumes and a smaller, nearly significant mean decrease in left hippocampal volume, compared with the placebo-treated patients. Other studies revealed that the diversity of clinical responses to donepezil therapy in AD is associated with regional cerebral blood flow (rCBF) changes, mainly in the frontal lobe (Shimizu et al 2006). Furthermore, there is a parallelism between cognitive improvement and increase in brain M1 muscarinic receptor binding after treatment with donepezil in AD (Kemp et al 2003). AChE activity also decreases in the CSF of patients treated with donepezil, but changes in other biomarkers, such as BuChE activity, β -amyloid (1–42), tau and phosphorylated tau proteins are not affected by donepezil treatment (Parnetti et al 2002).

In summary, it appears that donepezil is beneficial (in a dose-dependent manner) when assessed using global and cognitive outcome measures in AD; however, by finding the mean effect sizes of the treatment on the outcome measures of cognition from 8 empirical studies, it was determined that neither donepezil nor other AChEIs were greatly efficacious (Harry and Zakzanis 2005). Over 770 million days of patient use and an extensive publication database demonstrate that donepezil has a good tolerability and safety profile (Jackson et al 2004). The use of AChEIs in AD is currently appraised by the National Institute for Clinical Evidence (NICE). In a recent review providing the latest, best quality evidence of the effects of AChEIs on cognition, quality of life and

adverse events in people with mild to moderately-severe AD (m/sAD), Takeda et al (2006) stated (on a systemic review of 26 RCTs) that AChEIs can delay cognitive impairment in m/sAD for at least 6 months duration; however, results from head to head comparisons are limited by the low number of studies and the study quality. The Cochrane Database Reviewers conclude that people with mAD or sAD treated for periods of 12, 24, or 52 weeks with donepezil experienced benefits in cognitive function, activities of the daily living and behavior. Study clinicians rated global clinical state more positively in treated patients, and measured less decline in measures of global disease severity (Birks and Harvey 2006). In general terms, there is not robust support for any AChEI because the treatment effects are small and are not always apparent in practice (Birks and Harvey 2006; Takeda et al 2006). Donepezil treatment may be associated with reduced mortality in nursing home residents with dementia (Gasper et al 2005) and with delayed nursing home placement (Geldmacher et al 2003), although some authors denied that donepezil was able to reduce the rate of institutionalization or disability in mAD (Courtney et al 2004; Standridge 2004). The meta-analysis of caregiver-specific outcomes in antidementia clinical trials revealed that AChEIs have a small beneficial effect on burden and active time use among caregivers of persons with AD (Lingler et al 2005).

Mild cognitive impairment

Mild cognitive impairment (MCI) is the postulated transitional state between the cognitive changes of normal aging and early AD (Petersen et al 1999, 2005). The rate of progression to clinically diagnosable AD is 10%–15%/year among persons who meet the criteria for the amnesic form of MCI, in contrast to a rate of 1–2%/year among normal elderly persons (Petersen et al 1999). This is a clinical concept and instrumental aid invented to substitute the lack of accurate biological markers able to predict the risk of suffering AD. Despite its questionable value, it is important to keep in mind that neurodegeneration starts many years before the onset of the disease (Cacabelos et al 2005). It is very likely that AD neurons begin their deceasing process 20–40 years prior to the appearance of the first symptoms (eg, memory deficit, behavioral changes, functional decline, subtle praxis-related psychomotor alterations). In some patients with a specific genetic profile, it is possible to detect, by means of sensitive brain imaging techniques, a progressive brain dysfunction after the age of 30 years (Cacabelos 2003, 2005b). In this regard, it is clear that an early therapeutic intervention could be of some benefit for these patients precluding the possibility

of a premature neuronal death or delaying the onset of the disease for several years. AChEIs have been proposed as feasible candidate drugs for the treatment of MCI (Stirling Meyer et al 2002; Salloway et al 2003; Gauthier 2005).

Few studies have been performed with donepezil in MCI (Jelic et al 2005). In a double-blind, placebo-controlled, multicenter trial in US with 270 cases, a mild benefit in cognitive function has been reported (Salloway et al 2004). A Chinese group has performed a clinical trial with donepezil (2.5 mg/day for 3 months) in patients with amnesic MCI and found a significant improvement in cognitive performance as well as changes in the hippocampus as assessed by magnetic resonance spectroscopy (MRS) (Wang et al 2004).

In a recent study, Petersen et al (2005) evaluated 769 subjects with the amnesic subtype of MCI in a randomized, double-blind study with donepezil (10 mg/day) or vitamin E (2000 IU/day) for 3 years. The overall rate of progression from MCI to AD was 16%/year (212 patients evolved into the AD condition). As compared with the placebo group, there were no significant differences in the probability of progression to AD in the vitamin E group or the donepezil group during the 3 years of treatment. The donepezil group had a reduced likelihood of progression to AD during the first 12 months of the study, with better results among APOE-4 carriers (Petersen et al 2005).

The proposed benefit of AChEI therapy as a preventive strategy in MCI or as a regular option for people requesting some medication for memory improvement is far from clear and probably poses some underestimated dangers, despite the optimistic position of some authors (Jelic et al 2005). It has been observed that neuropsychological test performance deteriorates in healthy elderly volunteers receiving donepezil for 2 weeks; worsening is significant on tests of speed, attention, and short-term memory as compared with the placebo group, suggesting a perturbation of an already optimized cholinergic system in healthy subjects (Beglinger et al 2005). If the rate of conversion from MCI into AD is about 10%–15% per year, it is probably irresponsible to sacrifice 80% MCI cases to pyrrhically protect only 10% assuming that AChEIs in healthy subjects may induce undesirable cognitive effects.

The postulated long-lasting effects of AChEIs for 1–5 years (Doody et al 2001b; Bullock and Dengiz 2005; Giacobini 2006) were never clearly documented in well-controlled trials. In a recent study, Winblad et al (2006b) provide some support to the long-lasting efficacy and safety of donepezil after 3 years of treatment. In a cohort of 286 patients, there was a trend for patients receiving continuous therapy to have less global deterioration on the Gottfries-Brane-Steen scale

than those who had delayed treatment. Small but statistically significant differences between the groups were observed for the secondary measures of cognitive function (MMSE scores) and cognitive and functional abilities (GDS) in favor of continuous donepezil therapy (Winblad et al 2006b).

On a pathogenic basis, there is no evidence that AChEIs protect neurons against AD-related premature death. It might occur – as demonstrated with multifactorial therapies in AD (Cacabelos et al 2004c) – that cognitive enhancement induced by AChEI administration is the result of forcing surviving neurons to overwork for a period of time after which neurons become exhausted with the subsequent acceleration of their metabolic decline. This phenomenon has been demonstrated after administration of a combination therapy with CDP-choline, piracetam, and metabolic supplementation (Cacabelos et al 2004c). Under this therapeutic protocol, AD patients clearly improved for the first 9 months of treatment, and a progressive decline in therapeutic efficacy has been observed thereafter (Cacabelos et al 2004c; Cacabelos 2003, 2005a, b). The study of Petersen et al (2005) might be a good paradigm to illustrate the same phenomenon with donepezil in MCI patients who showed a positive response during the first year of treatment and no effect after 3 years. Taking into account these observations, we should be very cautious with the administration of pharmaceuticals (as a preventive strategy) to patients with MCI until a clear long-lasting efficacy of the therapeutic options can be demonstrated. This is especially important when some studies reveal that chronic administration of AChEIs (eg, galantamine) may even increase mortality (Scheltens et al 2004; Kirshner 2005).

Combination therapies

Combination drug therapy is the standard of care for treating many neuropsychiatric disorders and other medical conditions (eg, cardiovascular disease, hypertension, cancer, AIDS, diabetes). For the past 20 years, the pharmaceutical industry and the medical community have made a show of reluctance to treat AD with a combination therapy, but in fact most patients with dementia have been receiving an average of 6–9 different drugs per day in an attempt to control the multifaceted expressions of dementia. Multifactorial therapy, combining several types of drugs with potential neuroprotective effect on the CNS, has been tried in AD and other forms of dementia with promising results (Cacabelos et al 2000a b; Cacabelos 2002a b; Cacabelos 2003; Cacabelos et al 2004c; Cacabelos 2005a, b; Cacabelos et al 2006). Donepezil has been given in combination with other substances to patients with AD. Probably the best evidence-based combination

strategy is the addition of memantine to stable donepezil therapy in m/sAD (Tariot et al 2004; van Dyck et al 2006). This combination was found to benefit cognition, behavior, and activities of daily living. It appears that memantine in combination with donepezil is significantly better than donepezil alone in the management of behavioral symptoms (Tariot et al 2004; Xiong and Doraiswamy 2005; Doody 2005). Combination therapy with donepezil and memantine in healthy subjects did not show any significant alteration in pharmacokinetic or pharmacodynamic parameters of both drugs, suggesting that donepezil and memantine may be safely and effectively used in combination (Periclou et al 2004). According to basic studies using the whole-cell patch-clamp technique with multipolar neurons, the combination of donepezil and memantine might be a contradiction since donepezil potentiates NMDA currents (Moriguchi et al 2005) and memantine acts as a partial NMDA antagonist (Cacabelos et al 1999).

Combination therapy of donepezil (5 mg/day) with ginkgo biloba (90 mg/day) for 30 days did not show any significant difference in cognitive performance, pharmacokinetics and pharmacodynamics of donepezil, indicating that ginkgo supplementation does not have major impact on donepezil therapy (Yasui-Furukori et al 2004). Donepezil has also been given in combination with acetyl-L-carnitine (ALC) in AD. The addition of ALC to donepezil increased the response rate from 38% (AChEI alone) to 50% (AChEI + ALC) (Bianchetti et al 2003). Initial data resulting from combination studies of donepezil and vitamin E indicated that this long-term combination might be beneficial for AD (Klatte et al 2003).

Donepezil plus sertraline did not show any advantage over donepezil alone in AD, although the combination appeared to be beneficial in a subgroup of patients with moderate-to-severe behavioral and psychological symptoms (Finkel et al 2004). In patients with psychotic symptoms and lack of improvement of their delusions/hallucinations during perphenazine treatment, donepezil may reduce psychotic symptoms, suggesting that donepezil augmentation of neuroleptics (risperidone, olanzapine, quetiapine) may be appropriate for those patients for whom neuroleptic monotherapy either does not lead to symptom remission or is associated with intolerable side-effects (Bergman et al 2003). In some cases the combination of donepezil and neuroleptics may exacerbate extrapyramidal side-effects (Liu et al 2002). In general, combination therapy tends to show better results than monotherapy with one AChEI or any other single drug for dementia (Cacabelos 2002a, b; Cacabelos et al 2004c; Cacabelos 2005a, b). Similar results can be seen in animal

models when donepezil is given in combination with other compounds (Sonkusare et al 2005).

Comparative studies

Comparative studies with different AChEIs did not show any significant difference or traces of superiority among them in AD patients (Wilkinson et al 2002; Ritchie et al 2004; Aguglia et al 2004; Bullock et al 2005; Harry and Zakzanis 2005). In independent studies, there are apparent differences in ADAS-Cog changes, improvement rate, drop-outs, and incidence of side-effects among different classes of AChEIs; however, since the clinical protocols vary from one study to another, these results are not comparable and unreliable. In a number of studies analysed by Giacobini (2006) comparing 7 AChEIs, the ADAS-Cog variation vs placebo (AD/P) was 4.0–5.3/0.8–2.8 with tacrine, 4.7/1.83 with eptastigmine, 2.8–4.6/0.7–1.2 with donepezil, 1.9–4.9/0.7–1.2 with rivastigmine, 2.8–3.2/0.5–0.75 with metrifonate, and 3.1–3.9/1.73 with galantamine. About 30%–50% of patients improved with tacrine, 40%–58% with donepezil, 25%–37% with rivastigmine, 35%–40% with metrifonate, and 10%–23% with galantamine. The drop-out rate was 55%–73% in patients treated with tacrine, 35% with eptastigmine, 5%–13% with donepezil, 15%–36% with rivastigmine, 2%–28% with metrifonate, and 10%–13% with galantamine. Side-effects were more prevalent in patients treated with tacrine (40%–58%) than with the other AChEIs (donepezil, 6%–13%; rivastigmine, 15%–28%; metrifonate, 2%–12%; galantamine, 13%–16%) (Giacobini 2006). In clinical terms, according to Birks (2006), despite the slight variations in the mechanism of action of donepezil, rivastigmine, and galantamine, there is no evidence of any substantial differences between them with respect to efficacy; even though there appears to be less adverse effects associated with donepezil compared with rivastigmine (Birks 2006).

Effects on behavioral symptoms and functional deficits

Dementia is clinically characterized by memory disorders, behavioral changes, and progressive functional decline. The estimated prevalence of psychiatric symptoms in AD accounts for 40%–60% of the cases (Cacabelos et al 1996; Cacabelos et al 1997). In cross-sectional studies it has been reported that several psychiatric symptoms are associated with lower total MMSE scores and overall cognitive deterioration. Psychotic symptoms, especially delusions, hallucinations and misidentifications, are positively correlated with aggressive behavior and institutionalization. Agitation

and wandering are also associated with rapid cognitive decline in dementia. In general, psychotic symptoms parallel an accelerated cognitive deterioration, partially induced by psychotropic drugs in some cases or by many other classes of drugs currently used by patients in geriatric long-term settings (Arinzon et al 2006). In other cases, behavioral changes do not seem to be associated with exogenous factors and might be intrinsic to cortical atrophy and selective brain damage in dementia. The prevalence of psychotic symptoms in AD ranges from 15% to 50%, constituting a very common problem which is not always reduced by conventional antipsychotic or antianxiety drugs. In addition, antipsychotics may increase the risk of cerebrovascular accidents and also contribute to cortical atrophy after years of chronic treatment (Cacabelos et al 1996, 1997; Gill et al 2005). Furthermore, behavioral symptoms in AD significantly increase direct costs of care (US\$10,670–16,141 higher annual costs in high-NPI as compared with low-NPI) (Murman et al 2002). Several studies with AChEIs indicate that these compounds may exert a beneficial effect on some neuropsychiatric symptoms such as delusions, hallucinations, apathy, psychomotor agitation, depression and anxiety (Levy et al 1999; Trinh et al 2003). It is likely that AChEIs interact with atypical neuroleptics to synergistically increase the antipsychotic effect, this allowing a potential reduction in the dose of neuroleptics (Weiser et al 2002). What has to be demonstrated is that this pharmacodynamic interaction is common to all AChEIs, because it can not be excluded that some AChEIs may also precipitate psychotic symptoms and exacerbate extrapyramidal side-effects when given in combination with neuroleptics (eg, donepezil + risperidone) (Liu et al 2002).

Several papers have documented the parallel beneficial effects of donepezil on cognition and behavioral symptoms in AD (Matthews et al 2000; Tariot et al 2001; Paleacu et al 2002; Gauthier et al 2002a; Gauthier et al 2002b; Holmes et al 2004) (Table 2). In clinical trials, sleep problems have been identified as side-effects of donepezil. Poor sleep quality can exacerbate behavioral problems among patients and add to the burden experienced by caregivers. In a community-based study, the use of hypnotics was higher in donepezil users (9.78%) compared with non-users (3.93%) (Stahl et al 2003). Behavioral symptoms are a major problem in AD and, assuming that most psychotropic drugs contribute to deteriorate cognition and psychomotor function, as well as cerebrovascular function (Maguire 2000; Gill et al 2005), AChEIs represent an option to be explored in more detail as a monotherapy or in combination with other psychotropic agents at low doses (Barak et al 2001; Masterman 2004).

Donepezil in vascular dementia

Cerebrovascular dysfunction is a common finding in dementia; and mixed dementia (MXD) (degenerative + vascular) is the most frequent form of dementia in older patients (> 75–80 years) (Cacabelos 2003; Cacabelos et al 2003, 2004a, b). Diverse vascular risk factors (cardiovascular disorders, hypertension, hypotension, hypercholesterolemia, dyslipidemia, atherosclerosis, diabetes) accumulate in patients with dementia and are at the basis of the pathogenic mechanisms leading to vascular dementia (VD) (Cacabelos 2003; Cacabelos et al 2003; Cacabelos 2004a).

Studies with donepezil (Black et al 2003; Wilkinson et al 2003), and other AChEIs (Erkinjuntti et al 2002), have shown modest effects in VD. Improvements have been observed in cognition, behavior, and activities of daily living in VD patients treated with donepezil in a similar fashion to those detected in AD (Erkinjuntti et al 2002; Black et al 2003; Goldsmith and Scott 2003; Wilkinson et al 2003; Blasko et al 2004; Erkinjuntti et al 2004; Roman 2004; Roman et al 2005). The combined analysis of 2 identical randomized, double-blind, placebo-controlled, 24-week studies involving 1219 patients enrolled at 109 investigational sites in the USA, Europe, Canada, and Australia, revealed that donepezil groups showed significant improvements in cognition, global function, and ADLs (Roman et al 2005). In post-marketing studies, donepezil in VD (sometimes called AD + cerebrovascular disease) patients appears to show similar benefits to those observed in AD patients in the areas of cognition, global function, and quality of life (Malouf and Birks 2004; Schindler 2005). The main features of VD patients included in donepezil studies were the following: 68% of patients had a history of at least one stroke, and 28% of patients had a history of transient ischemic attacks before dementia; 99% of cases exhibited cortical and subcortical infarcts; 73% of patients had experienced an abrupt onset of cognitive symptoms; and vascular risk factors were prominent and included hypertension (70%), smoking (62%), and hypercholesterolemia (39%) (Pratt 2005). In general, diagnostic criteria, inclusion criteria, outcome measures (psychometric and instrumental), and follow-up studies are deficient in clinical trials with VD patients; furthermore, many cases with minor cerebrovascular damage and vascular risk factors are currently included in AD trials and neglected in VD trials (Cacabelos et al 2003, 2004a, b).

An important cerebrovascular component is present in most AD cases older than 70–75 years of age, and most cases of dementia are of the mixed type in older patients (> 80 years) who exhibit a clear brain hypoperfusion pattern

as well as accumulation of vascular risk factors (Cacabelos 2003, 2004; Cacabelos et al 2003, 2004a, b). Glucose metabolism tends to decline over time in the bilateral precuneus and posterior cingulate gyri and in the frontal, temporal and parietal cortices of AD patients (Hirono et al 2004). Studies of regional cerebral blood flow (rCBF) as assessed by SPECT revealed that AD patients showed a preserved rCBF in the right and left anterior cingulate gyri, right middle temporal gyrus, right inferior parietal lobe, and prefrontal cortex after 1-year of treatment with donepezil (Nakano et al 2001). Significant rCBF reduction was observed in the temporal lobe and occipital-temporal cortex of the left hemisphere of untreated patients, whereas no significant change was observed in patients treated with donepezil for 1 year (Nobili et al 2002). In a small study ($n = 10$), patients with vascular dementia improved their cognitive function and the latency of the P300 auditory ERPs after one month of treatment with donepezil (Paci et al 2006). In another study with 15 VD patients, a marginal effect was observed on MMSE scores, with substantial gains on tests of working memory and delayed recognition memory (Thomas et al 2005). According to some Japanese authors, vascular lesions and related risk factors may influence responsiveness to donepezil in AD. For instance, high HDS-R (Revised-Hasegawa Dementia Scale), low CDT (Clock Drawing Test) scores, low CDR (Clinical Dementia Rating), and the presence of hypertension and periventricular hyperintensities predicted the profile of true responders (Fukui and Taguchi 2005). Others have found that antihypertensive medications in AD patients treated with AChEIs are associated with an independent improvement on cognition after 40 weeks of treatment (Rozzini et al 2005).

Side-effects and major adverse drug reactions (ADRs)

On average, side-effects in donepezil trials account for 20%–60% of dropouts and are present in 10%–70% of the patients depending upon type and severity of the ADRs. Side-effects and ADRs associated with donepezil can be classified in two main categories: common side-effects, most of them observed in clinical trials with AD patients, and unfrequent or extraordinary side-effects, seen in especial conditions or in small clusters of patients with different pathologies under treatment with other concomitant drugs. The most frequent ADRs (Table 3) occurring in more than 5% of patients treated with donepezil include body events (45%), cardiovascular problems (18%), alterations in the digestive system (34%), hematic and lymphatic alterations (5%), metabolic and

nutritional changes (6%), musculoskeletal problems (17%), complications in the respiratory system (22%), skin and appendages (14%), special senses (5%), urogenital (24%), and CNS (52%) (agitation, insomnia, confusion, depression, anxiety, dizziness, vertigo, headache, restlessness, hallucinations) (Bryson and Benfield 1997; Rogers 1998; Doody 1999; Nordberg and Svensson 1999; Wilkinson 1999; Dunn et al 2000; Greenberg et al 2000; Rogers et al 2000; Bentué-Ferrer et al 2003; Jackson et al 2004; Courtney et al 2004; Johannsen et al 2006). Other important side-effects observed in patients treated with donepezil include agitation, aggressive and violent behavior in AD and Down's syndrome; extrapyramidal symptoms and tardive dyskinesia in schizophrenia and psychotic disorders; catatonia in DLB; and a number of rare effects, such as athetosis, Pisa syndrome (pleurothonus) (Kwak et al 2000; Miyaoka et al 2001), a fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy in an 83-year-old woman (Verrico et al 2000), purpuric rash in an 82-year-old woman receiving long-term treatment with atenolol and doxazosin (Bryant et al 1998), hypnopompic hallucinations (Yorston and Gray 2000), urinary incontinence (Hashimoto et al 2000), extrapyramidal syndrome (Magnuson et al 1998; Carcenac et al 2000), seizures (Babic and Zurak 1999), pancreatitis, syncope (Greenberg et al 2000), mania (Benazzi 1999; Jacobsen and Comas-Diaz 1999), violent behavior (Bouman and Pinner 1998), and some other ADRs in isolated cases with different pathologies (Table 3).

Donepezil may adversely influence cardiovascular autonomic control (McLaren et al 2003). More than 40% of elderly subjects susceptible of treatment with AChEIs show some kind of cardiac dysfunction. Donepezil reduces mean heart rate, especially low (0.04–0.15 Hz) and high (0.15–0.40 Hz) frequency components of the ECG (1–30 sec modulation of heart rate variability) (Masuda and Kawamura 2003). In patients receiving donepezil for more than 1 year several cases of syncope have been reported. In 31% of the cases, no cause of syncope was found; and in 69% of the cases the cause of syncope was associated with carotid sinus syndrome, complete atrioventricular block, sinus node dysfunction, severe orthostatic hypotension and paroxysmal atrial fibrillation (Bordier et al 2005).

Another important issue in the prescription of AChEIs is the potential interaction of these agents with psychotropic drugs and other medications. Drug–drug interactions can be observed between donepezil and antidepressants such as serotonin uptake inhibitors (sertraline, paroxetine, fluoxetine) and tricyclics (imipramine, maprotiline), or with antipsychotics

(risperidone, olanzapine, quetiapine), antihistaminics, and anti-epileptics. Donepezil can aggravate extrapyramidal symptoms when co-administered with atypical antipsychotics (eg, risperidone). The cholinergic activity of some histamine H1 receptor antagonists or tricyclic antidepressants can be antagonized by donepezil. Despite all these theoretical possibilities, most studies reported to date demonstrate that drug–drug interactions with donepezil (memantine, risperidone, sertraline, levodopa, thioridazine, theophylline, furosemide, cimetidine, warfarin, digoxin, ginkgo biloba, piracetam, CDP-choline, anapsos, topiramate) do not show clinical relevance (Tiseo et al 1998a, b, c, d; Yasui-Furukori et al 2004; Nagy et al 2004; Okereke et al 2004; Periclou et al 2004; Ravic et al 2004; Reyes et al 2004; Seltzer 2005; Wheeler 2006), except in isolated cases (Magnuson et al 1998; Zhao et al 2003). The concurrent administration of ketoconazole and donepezil produces no change in ketoconazole plasma concentrations, but a statistically significant change in donepezil plasma concentrations. These changes might be associated with CYP2D6-related enzyme interactions (Tiseo et al 1998e). A case of malignant-like syndrome due to donepezil and maprotiline has been reported (Ohkoshi et al 2003). Another case of malignant syndrome has been reported in a 68-year-old Japanese patient with history of delusions and hallucination under treatment with bromperidol (12 mg) and donepezil (5 mg) (Ueki et al 2001). Donepezil may also interact with some anesthetics. It can not be excluded that donepezil act on muscle plaque, blocking acetylcholine hydrolysis and antagonizing atracurium, since in a 75-year-old AD patient undergoing left colectomy under general anesthesia, after 14 months of treatment with donepezil, succinylcholine-induced relaxation was markedly prolonged and the effect of atracurium besylate was inadequate even at very high doses (Sánchez Morillo et al 2003). Suxamethonium and donepezil may also be a cause of prolonged paralysis (Crowe and Collins 2003).

Recent findings indicate that donepezil users may experience changes in lipid profile. Statistically significant higher levels of triglycerides, cholesterol, LDL-cholesterol, and VLDL-cholesterol have been found in donepezil users as compared with non-users (Adunsky et al 2004). Moreover, high cholesterol levels correlated with faster decline at 1-year follow-up in AD patients on AChEI therapy (Borroni et al 2003). In this regard, it is important to keep in mind that alterations in lipid metabolism might represent an additional risk factor for dementia and that APOE-related cholesterol changes are currently seen in AD (Cacabelos 2003, 2004; Cacabelos et al 2004a, b). If donepezil-related cholesterol alterations are confirmed in well-controlled

trials, in which genotype-related patient stratification is highly recommended, then donepezil should be avoided in vulnerable cases.

Pharmacogenetics

With the advent of recent knowledge on the human genome (International Human Genome Sequencing Consortium 2004) and the identification and characterization of AD-related genes (Cacabelos et al 2005), as well as novel data regarding CYP family genes and other genes whose enzymatic products are responsible for drug metabolism in the liver (eg, NATs, ABCBs/MDRs, TPMT), it has been convincingly postulated that the incorporation of pharmacogenetic and pharmacogenomic procedures in drug development might bring about substantial benefits in terms of therapeutics optimization in dementia (Cacabelos 2002a, b; Cacabelos 2005a, b) and in many other complex disorders, assuming that genetic factors are determinant for both premature neuronal death in AD and drug metabolism (Cacabelos 2005a, b; Cacabelos et al 2005). With pharmacogenetics we can understand how genomic factors associated with genes encoding enzymes responsible for drug metabolism regulate pharmacokinetics and pharmacodynamics (mostly safety issues) (Evans and McLeod 2003; Weinshilboum 2003; Weinshilboum and Wang 2006). With pharmacogenomics we can differentiate the specific disease-modifying effects of drugs (efficacy issues) acting on pathogenic mechanisms directly linked to genes whose mutations determine alterations in protein synthesis or subsequent protein misfolding and aggregation (Cacabelos 2002a, b; Nebert and Jorge-Nebert 2002; Cacabelos 2003; Cacabelos 2005a, b). The capacity of drugs to reverse the effects of the activation of pathogenic cascades (phenotype expression) regulated by networking genes basically deals with efficacy issues. The application of these procedures to dementia is a very difficult task, since dementia is a complex disorder in which more than 200 genes might be involved (Cacabelos et al 2005). In addition, it is very unlikely that a single drug be able to reverse the multifactorial mechanisms associated with premature neuronal death in most dementing processes with a complex phenotype represented by memory decline, behavioral changes, and progressive functional deterioration. This clinical picture usually requires the utilization of different drugs administered simultaneously, including memory enhancers, psychotropics (antidepressants, neuroleptics, anxiolytics), anticonvulsants, antiparkinsonians, and also other types of drugs of current use in the elderly due to the presence of concomitant ailments (eg, hypertension, cardiovascular disorders, diabetes, hypercholesterolemia).

Although drug effect is a complex phenotype that depends on many factors, it is estimated that genetics accounts for 20%–95% of variability in drug disposition and pharmacodynamics (Weinshilboum 2003). Cholinesterase inhibitors of current use in AD, such as donepezil and rivastigmine (and tacrine, as well) are metabolized via CYP-related enzymes (Table 1). These drugs can interact with many other drugs which are substrates, inhibitors or inducers of the cytochrome P-450 system, this interaction eliciting liver toxicity and other adverse drug reactions (ADRs) (Cacabelos 2005a, b) (Tables 1 and 3). Many of these substances are metabolized by enzymes known to be genetically variable, including: (a) esterases: butyrylcholinesterase, paraoxonase/arylesterase; (b) transferases: N-acetyltransferase, sulfotransferase, thiol methyltransferase, thiopurine methyltransferase, catechol-O-methyltransferase, glutathione-S-transferases, UDP-glucuronosyltransferases, glucosyltransferase, histamine methyltransferase; (c) reductases: NADPH:quinine oxidoreductase, glucose-6-phosphate dehydrogenase; (d) oxidases: alcohol dehydrogenase, aldehydehydrogenase, monoamine oxidase B, catalase, superoxide dismutase, trimethylamine N-oxidase, dihydropyrimidine dehydrogenase; and (e) cytochrome P450 enzymes, such as CYP1A1, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A5, and many others (Kalow and Grant 2001). Polymorphic variants in these genes can induce changes in drug metabolism altering the efficacy and safety of the prescribed drugs. Drug metabolism includes phase I reactions (ie, oxidation, reduction, hydrolysis) and phase II conjugation reactions (ie, acetylation, glucuronidation, sulfation, methylation). The typical paradigm for the pharmacogenetics of phase I drug metabolism is represented by the cytochrome P450 enzymes, a superfamily of microsomal drug-metabolizing enzymes. P450 enzymes represent a superfamily of heme-thiolate proteins widely distributed in bacteria, fungi, plants and animals. The P450 enzymes are encoded in genes of the CYP superfamily and act as terminal oxidases in multicomponent electron transfer chains which are called P450-containing monooxygenase systems. Some of the enzymatic products of the CYP gene superfamily can share substrates, inhibitors and inducers whereas others are quite specific for their substrates and interacting drugs (Nebert and Jorge-Nebert 2002; Evans and McLeod 2003).

The principal enzymes with polymorphic variants involved in phase I reactions are the following: CYP3A4/5/7, CYP2E1, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2, epoxide hydrolase, esterases, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase),

ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase). The microsomal, membrane-associated, P450 isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2E1, and CYP1A2 are responsible for the oxidative metabolism of more than 90% of marketed drugs; and CYP3A4 metabolizes more drug molecules than all other isoforms together. Major enzymes involved in phase II reactions include the following: UGTs (uridine 5'-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT (catechol-O-methyltransferase), HMT (histamine methyl-transferase), STs (sulfotransferases), GST-A (glutathione S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others (Kalow and Grant 2001). Most of these polymorphic genes exhibit geographic and ethnic differences. These differences influence drug metabolism in different ethnic groups in which drug dosage should be adjusted according to their enzymatic capacity, differentiating normal or extensive metabolizers (EMs), poor metabolizers (PMs) and ultrarapid metabolizers (UMs) (Cacabelos 2005a, b).

It is very well known for many years the heterogeneity of AD and how apparently identical phenotypes assessed with international clinical criteria (NINCDS-ADRDA, DSM-IV, ICD-10) do not always respond to the same drugs (Cacabelos et al 2000a, b; Cacabelos 2005a, b). This may be due to different factors, including pharmacokinetic and pharmacodynamic properties of drugs, nutrition, liver function, concomitant medications, and individual genetic factors (Cacabelos 2005b). In fact, the therapeutic response of AD patients to conventional cholinesterase inhibitors is partially effective in only 10%–20% of the cases, with side-effects, intolerance, and non-compliance in more than 60% of the patients due to different reasons (eg, efficacy, safety) (Giacobini 2000, 2006; Cacabelos et al 2000b). Therefore, the individualization of therapy or pharmacological tailoring in AD and other CNS disorders is just a step forward of the longstanding goal of molecular pharmacogenomics taking advantage from the information and procedures provided by the sequencing of the entire human genome (International Human Genome Sequencing Consortium 2004).

Several studies indicate that the presence of the APOE-4 allele differentially affects the quality and size of drug responsiveness in AD patients treated with cholinergic enhancers (tacrine, donepezil, rivastigmine) (Poirier 1999; Poirier et al 1995; Almqvist et al 2001). For example, APOE-4 carriers show a less significant therapeutic response to tacrine (60%) than patients with no APOE-4 (Poirier et al 1995). In another study the frequency of APOE-4 alleles

was higher in responders to a single oral dose of tacrine (Almqvist et al 2001). More than 80% of APOE-4(-) AD patients showed marked improvement after 30 weeks of treatment with tacrine, whereas 60% of APOE-4(+) carriers had a poor response (Poirier et al 1995). Others found no differences after 6 months of treatment with tacrine among APOE genotypes, but after 12 months the CIBIC scores revealed that APOE-4 carriers had declined more than the APOE-2 and APOE-3 patients, suggesting that a faster rate of decline was evident in the APOE-4 patients probably reflecting that APOE-4 inheritance is a negative predictor of treatment of tacrine in AD (Sjögren et al 2001). It has also been shown that the APOE genotype may influence the biological effect of donepezil on APP metabolism in AD (Borroni et al 2002). Prospective studies with galantamine in large samples of patients in Europe (Aerssens et al 2001) and in USA (Raskind et al 2000) showed no effect of APOE genotypes on drug efficacy, but a retrospective study with a small number of AD cases in Croatia showed the intriguing result of 71% responders to galantamine treatment among APOE-4 homozygotes (Babic et al 2004). MacGowan et al (1998) reported that gender is likely to be a more powerful determinant of outcome of anticholinesterase treatment than APOE status in the short term. In contrast, other studies do

not support the hypothesis that APOE and gender are predictors of the therapeutic response of AD patients to tacrine or donepezil (Rigaud et al 2002). In a recent study, Petersen et al (2005) showed that APOE-4 carriers exhibited a better response to donepezil. Similar results have been found by Bizzarro et al (2006); however, Rigaud et al (2002) did not find any significant difference between APOE-4-related responders and non-responders to donepezil. An APOE-related differential response has also been observed in patients treated with other compounds devoid of acetylcholinesterase inhibiting activity (CDP-choline, anapsos) (Alvarez et al 1999; Alvarez et al 2000) suggesting that APOE-associated factors may influence drug activity in the brain either directly acting on neural mechanisms or indirectly influencing diverse metabolic pathways. To date, few studies have addressed in a prospective manner the impact of pharmacogenetic and pharmacogenomic factors on AD therapeutics; however, recent data indicate that the therapeutic response in AD is genotype-specific (Cacabelos et al 2000a, b; Cacabelos 2002a, b; Cacabelos 2003; Cacabelos et al 2004b; Cacabelos 2005a, b).

CYP2D6-related therapeutic response

The CYP2D6 enzyme, encoded by a gene that maps on 22q13.1-13.2, catalyzes the oxidative metabolism of more than

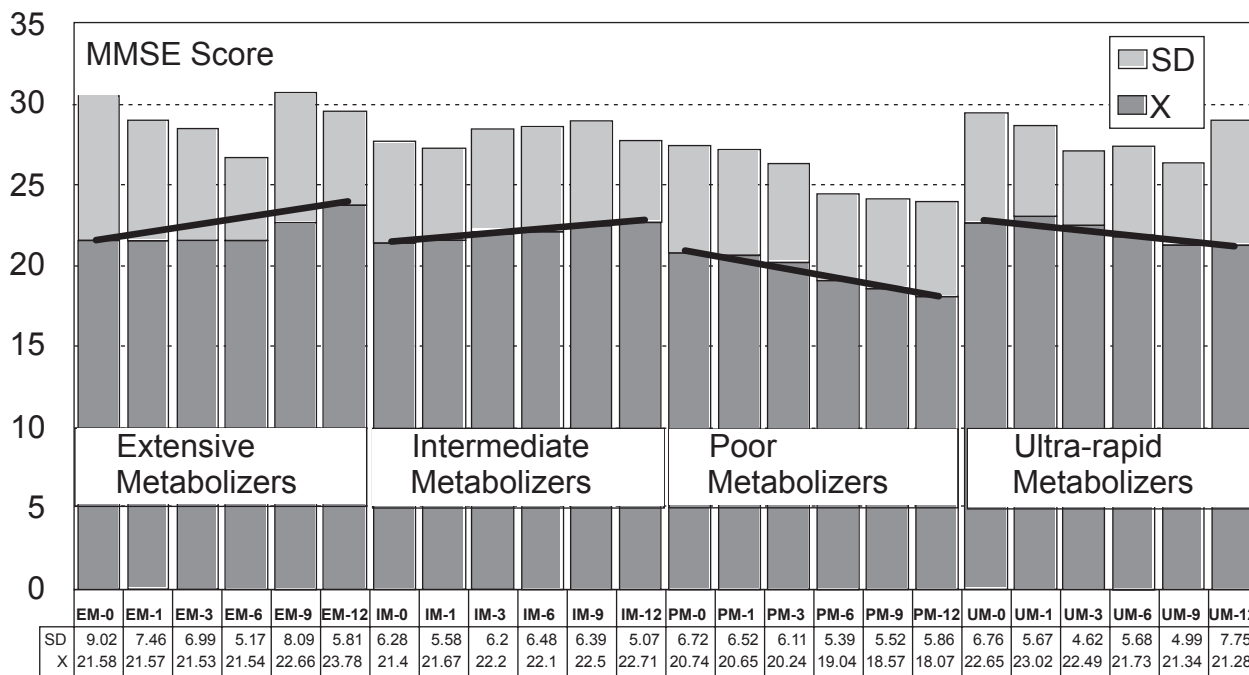


Figure 1 CYP2D6-related therapeutic response in Alzheimer's disease. Cognitive performance in extensive (EM), intermediate (IM), poor (PM), and ultra-rapid metabolizers (UM) during treatment with a multifactorial (combination) therapy.

Notes and abbreviations: MMSE, Mini-Mental State Examination; 0, Baseline Score (prior to treatment); 1-12, 1-12 months of treatment; SD, standard deviation; X, mean (MMSE score).

100 clinically important and commonly prescribed drugs such as cholinesterase inhibitors (tacrine, donepezil, galantamine), antidepressants, neuroleptics, opioids, some β -blockers, class I antiarrhythmics, analgesics and many other drug categories, acting as substrates, inhibitors or inducers with which cholinesterase inhibitors may potentially interact, this leading to the outcome of ADRs (Cacabelos 2005a, b). The CYP2D6 locus is highly polymorphic, with more than 100 different CYP2D6 alleles identified in the general population showing deficient (poor metabolizers, PM), normal (extensive metabolizers, EM) or increased enzymatic activity (ultra-rapid metabolizers, UM). Most individuals (> 80%) are EMs; however, remarkable interethnic differences exist in the frequency of the PM and UM phenotypes among different societies all over the world (Isaza et al 2000; Cacabelos and Takeda 2006). On the average, approximately 6.28% of the world population belongs to the PM category. Europeans (7.86%), Polynesians (7.27%), and Africans (6.73%) exhibit the highest rate of PMs, whereas Orientals (0.94%) show the lowest rate. The frequency of PMs

among Middle Eastern populations, Asians, and Americans is in the range of 2%–3% (Isaza et al 2000; Cacabelos 2005a, b; Cacabelos and Takeda 2006).

The most frequent CYP2D6 alleles in the European population are the following: CYP2D6*1 (wild-type) (normal), CYP2D6*2 (2850C>T) (normal), CYP2D6*3 (2549A>del) (inactive), CYP2D6*4 (1846G>A) (inactive), CYP2D6*5 (gene deletion) (inactive), CYP2D6*6 (1707T>del) (inactive), CYP2D6*7 (2935A>C) (inactive), CYP2D6*8 (1758G>T) (inactive), CYP2D6*9 (2613-2615 delAGA) (partially active), CYP2D6*10 (100C>T) (partially active), CYP2D6*11 (883G>C) (inactive), CYP2D6*12 (124G>A) (inactive), CYP2D6*17 (1023C>T) (partially active), and CYP2D6 gene duplications (with increased or decreased enzymatic activity depending upon the genes involved) (Cacabelos 2007).

EMs are more prevalent in AD (*1/*1, 49.42%; *1/*10, 8.04%) (total AD-EMs: 57.47%) than in controls (*1/*1, 44.12%; *1/*10, 0%) (total C-EMs: 44.12%). In contrast, IMs

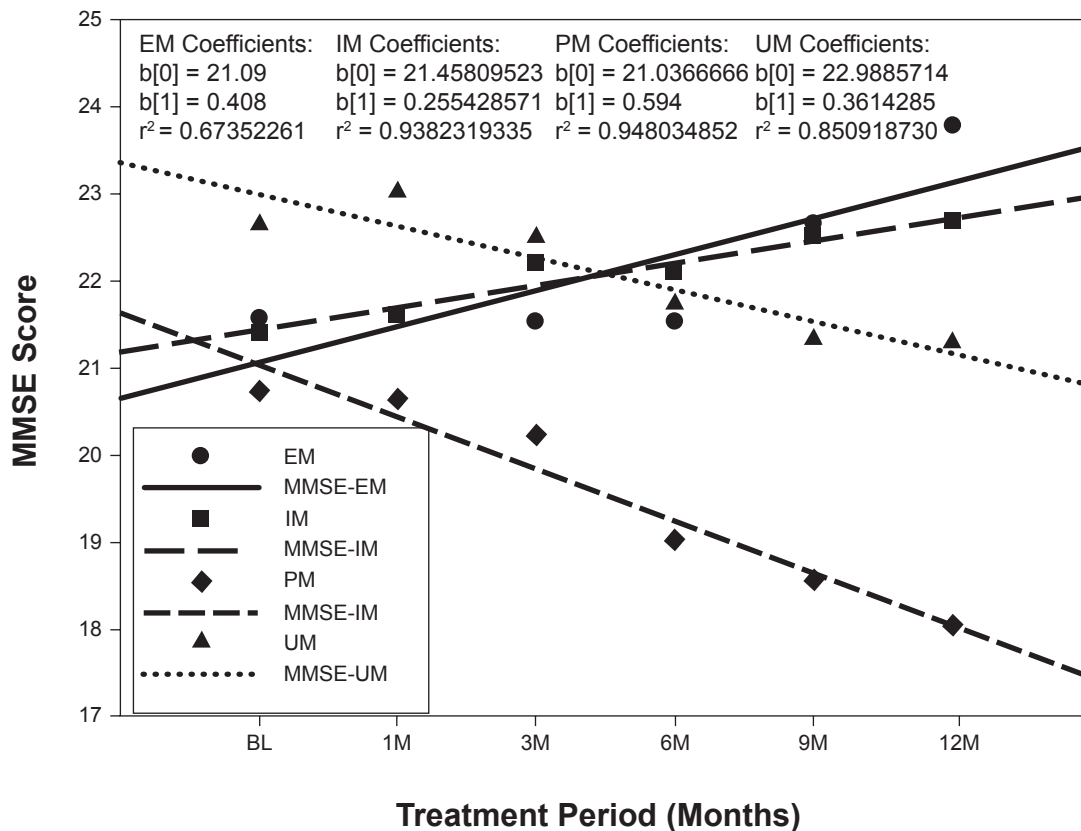
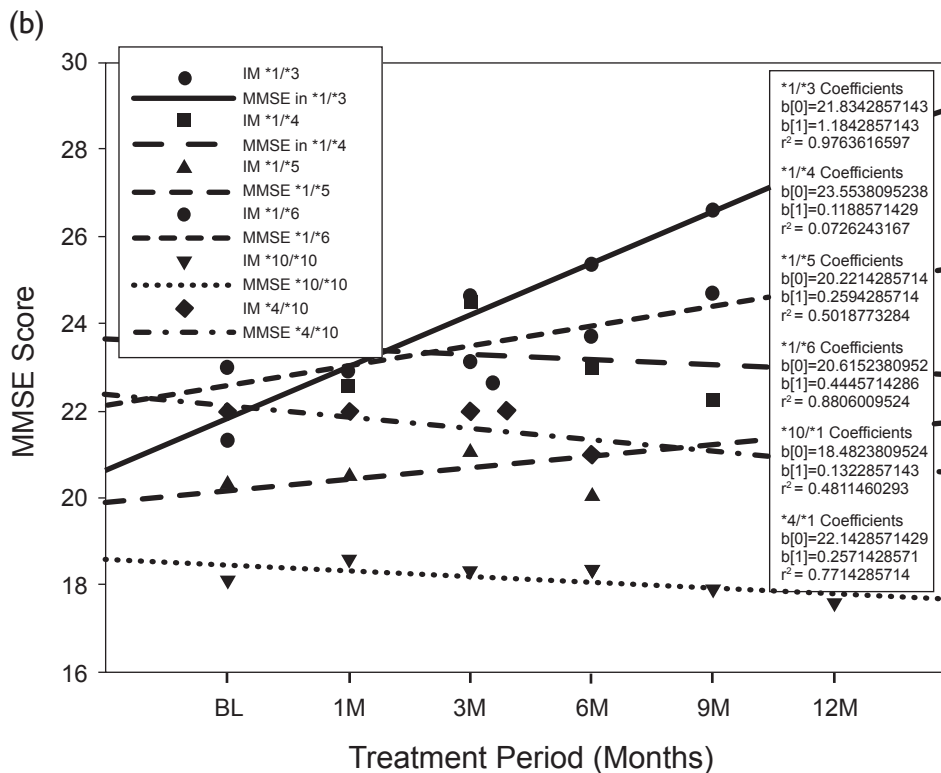
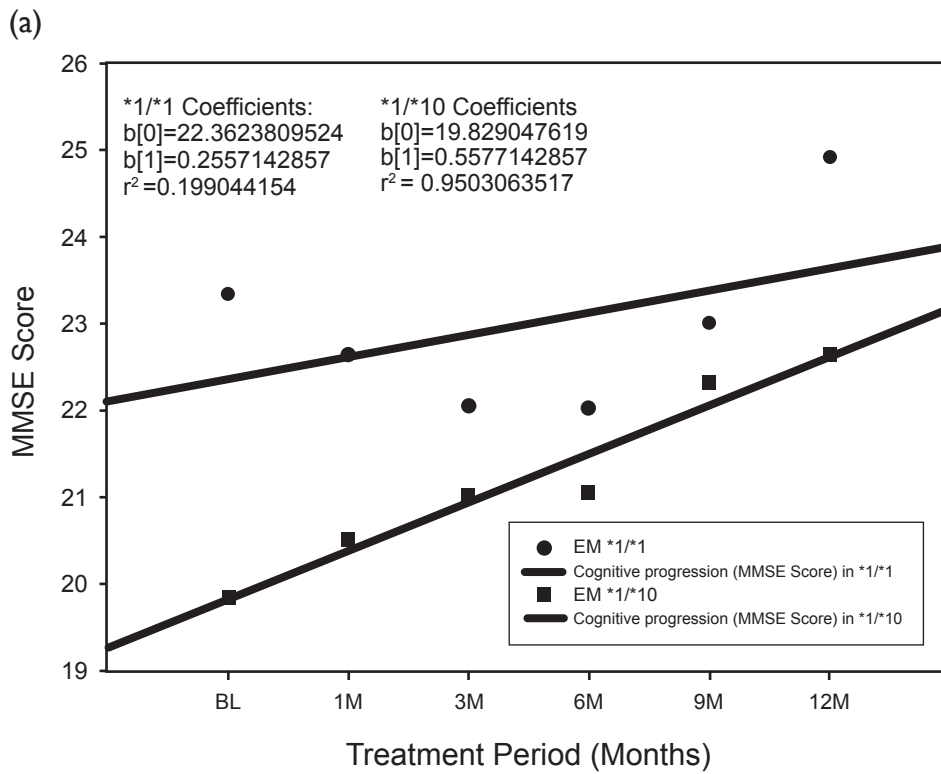


Figure 2 CYP2D6-related cognitive performance in Alzheimer's disease. Correlation analysis among CYP2D6-related extensive (EM), intermediate (IM), poor (PM), and ultra-rapid metabolizers (UM) to characterize responders and non-responders during 1-year treatment period with a multifactorial therapy.



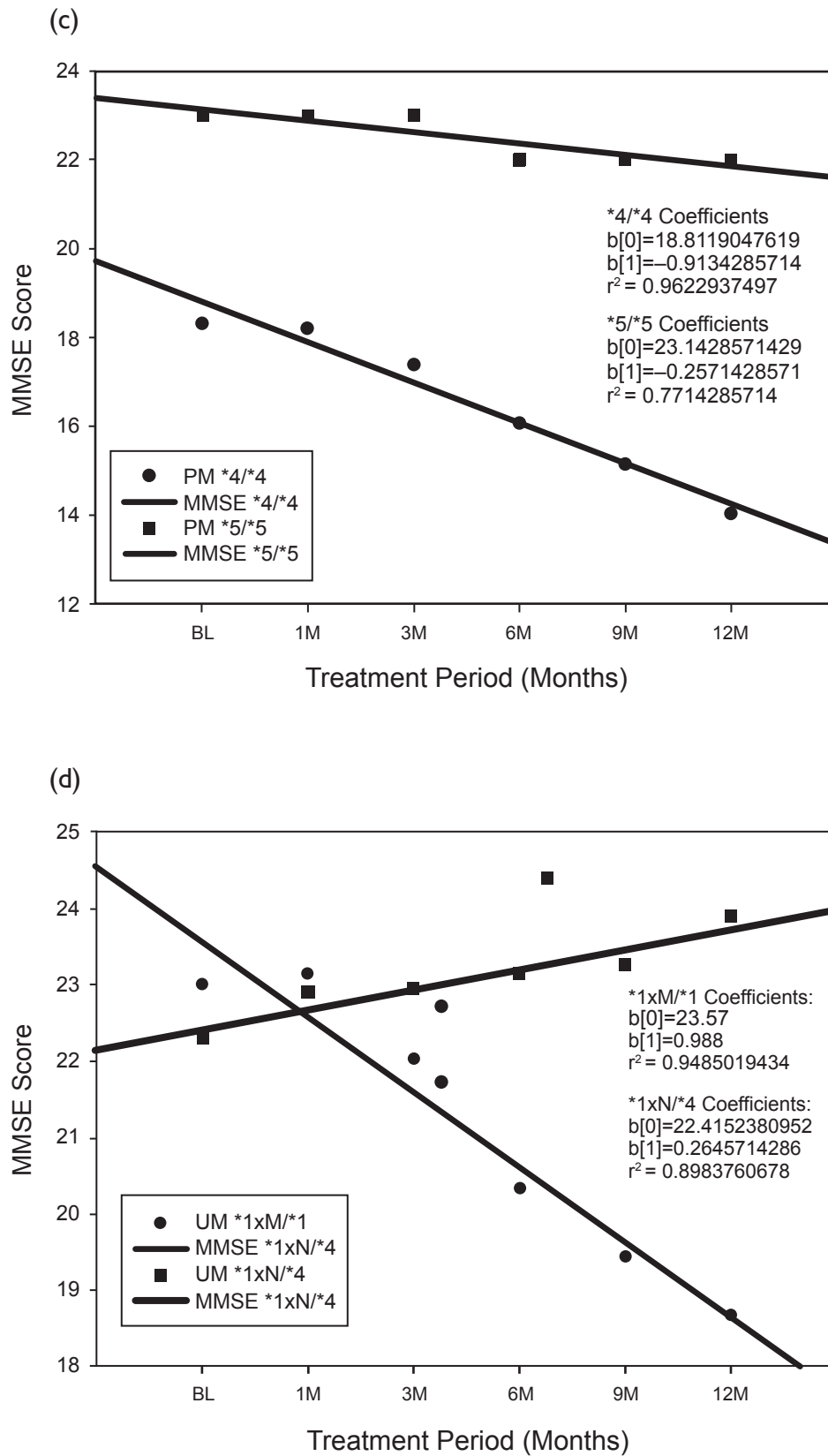


Figure 3 CYP2D6-related therapeutic response in Alzheimer's disease. Influence of CYP2D6 genotypes on cognitive performance during treatment with a multifactorial therapy (CDP-choline, 500 mg/day; piracetam, 1600 mg/day; nicergoline, 5 mg/day; donepezil, 5 mg/day). (a) Extensive Metabolizers (EM); (b) Intermediate Metabolizers (IM); (c) Poor Metabolizers (PM); (d) Ultra-rapid Metabolizers (UM).

are more frequent in controls (41.18%) than in AD (25.29%), especially the *1/*4 (C: 23.53%; AD: 12.64%) and *4/*10 genotypes (C: 5.88%; AD: 1.15%). The frequency of PMs was similar in AD (9.20%) and controls (8.82%), and UMs were more frequent among AD cases (8.04%) than in controls (5.88%) (Cacabelos 2007).

The genetic variation between AD and controls associated with CYP2D6 genotypes is 13.35% in EMs, 15.89% in IMs, 0.38% in PMs, and 2.16% in UMs, with an absolute genetic variation of 31.78% between both groups, suggesting that this genetic difference might influence AD pathogenesis and therapeutics (Cacabelos 2007).

In the first CYP2D6-related pharmacogenetic study with a combination therapy (donepezil + CDP-choline + piracetam + nicergoline) in AD, EMs improved their cognitive function (MMSE score) from 21.58 ± 9.02 at baseline to 23.78 ± 5.81 after 1-year treatment ($r = +0.82$; a Coef. = +20.68; b Coef.: +0.4). IMs also improved from 21.40 ± 6.28 to 22.50 ± 5.07 ($r = +0.96$; a Coef. = +21.2; b Coef. = +0.25), whereas PMs and UMs deteriorate from 20.74 ± 6.72 to 18.07 ± 5.52 ($r = -0.97$; a Coef. = +21.63; b Coef. = -0.59), and from 22.65 ± 6.76 to 21.28 ± 7.75 ($r = -0.92$; a Coef. = +23.35; b Coef. = -0.36), respectively. According to these results, PMs and UMs were the worst responders, showing a progressive cognitive decline with no therapeutic effect, and EMs and IMs were the best responders, with a clear improvement in cognition after 1 year of treatment (Figures 1, 2). Among EMs, AD patients harbouring the *1/*10 genotype ($r = +0.97$; a Coef. = +19.27; b Coef. = +0.55) responded better than patients with the *1/*1 genotype ($r = +0.44$; a Coef. = +22.10; b Coef. = +0.25). The best responders among IMs were the *1/*3 ($r = +0.98$; a Coef. = +20.65; b Coef. = 1.18), *1/*6 ($r = 0.93$; a Coef. = +22.17; b Coef. = +0.44) and *1/*5 genotypes ($r = +0.70$; a Coef. = +19.96; b Coef. = +0.25), whereas the *1/*4, *10/*10, and *4/*10 genotypes were poor responders. Among PMs and UMs, the poorest responders were carriers of the *4/*4 ($r = -0.98$; a Coef. = +19.72; b Coef. = -0.91) and *1xN/*1 genotypes ($r = -0.97$; a Coef. = +24.55; b Coef. = -0.98), respectively (Figure 3). The CYP2D6-related therapeutic responses can be modified by the presence of the APOE-4/4 genotype which converts EMs and IMs in poor responders (Cacabelos 2007).

From this study, we can conclude the following: (1) there is an accumulation of AD-related genes of risk in PMs and UMs; (2) PMs and UMs tend to show higher transaminase activities than EMs and IMs; (3) EMs and IMs are the best responders, and PMs and UMs are the worst

responders to a combination therapy with cholinesterase inhibitors, neuroprotectants, and vasoactive substances (Figures 1, 2, 3); (4) EMs and IMs can be converted into poor responders by the presence of the APOE-4/4 genotype; and (5) the pharmacogenetic response in AD appears to be dependent upon the networking activity of genes involved in drug metabolism and genes involved in AD pathogenesis (Cacabelos 2007).

Taking into consideration the available data, it might be inferred that at least 15% of the AD population may exhibit an abnormal metabolism of cholinesterase inhibitors and/or other drugs which undergo oxidation via CYP2D6-related enzymes. Approximately 50% of this population cluster would show an ultrarapid metabolism, requiring higher doses of cholinesterase inhibitors to reach a therapeutic threshold, whereas the other 50% of the cluster would exhibit a poor metabolism, displaying potential adverse events at low doses. If we take into account that approximately 60%–70% of therapeutic outcomes depend upon pharmacogenomic criteria (eg, pathogenic mechanisms associated with AD-related genes), it can be postulated that pharmacogenetic and pharmacogenomic factors are responsible for 75%–85% of the therapeutic response (efficacy) in AD patients treated with conventional drugs (Cacabelos et al 2000a, b; Cacabelos 2002a, b; Cacabelos 2003; Cacabelos et al 2004c; Cacabelos 2005a, b; Cacabelos 2006; Cacabelos 2007). Of particular interest are the potential interactions of cholinesterase inhibitors with other drugs of current use in patients with AD, such as antidepressants, neuroleptics, antiarrhythmics, analgesics, and antiemetics which are metabolized by the cytochrome P450 CYP2D6 enzyme (Bernard et al 2006). Although most studies predict the safety of donepezil and galantamine, as the two principal cholinesterase inhibitors metabolized by CYP2D6-related enzymes, no pharmacogenetic studies have been performed so far on an individual basis to personalize the treatment, and most studies reporting safety issues are the result of pooling together pharmacological and clinical information obtained with conventional procedures. In certain cases, genetic polymorphism in the expression of CYP2D6 is not expected to affect the pharmacodynamics of some cholinesterase inhibitors because major metabolic pathways are glucuronidation, O-demethylation, N-demethylation, N-oxidation, and epimerization. However, excretion rates are substantially different in EMs and PMs. For instance, in EMs, urinary metabolites resulting from O-demethylation of galantamine represent 33.2% of the dose compared with 5.2% in PMs, which show correspondingly higher urinary excretion of unchanged galantamine and its N-oxide (Mannens et al 2002). Therefore, still there are many unanswered questions

regarding the metabolism of cholinesterase inhibitors and their interaction with other drugs (potentially leading to ADRs) which require pharmacogenetic elucidation.

Conclusions

Donepezil is a piperidine-derivative reversible AChEI that enhances cholinergic neurotransmission and may have other non-cholinergic actions with potential benefit for dementia (Table 2). Main pharmacological properties of donepezil include the following (Tables 1): (1) after oral ingestion, peak plasma concentrations are achieved in 3–5 hours; (2) absorption is not affected by food; (3) linear pharmacokinetics over a dose range of 1–10 mg/day; (4) steady-state plasma concentration reached in 14–21 days with daily dosing; (5) mean steady-state plasma concentrations are dose proportional; (6) mean cerebral spinal fluid/plasma concentration is 0.157; (7) 96% of circulating donepezil is protein bound; (8) elimination half-life is approximately 70 hours; (9) it is mostly excreted unchanged in urine; (10) there is some CYP3A4- and CYP2D6-related metabolism; (11) there are not significant drug interactions; (12) the most important ADRs associated with donepezil are body events (45%), cardiovascular (18%), digestive (34%), hematic and lymphatic (5%), metabolic and nutritional (6%), musculoskeletal (17%), nervous system (52%), respiratory system (22%), skin and appendages (14%), special senses (5%), urogenital (25%), and some other rare side effects (1%–2%) (Table 3); (12) donepezil is effective in mAD and sAD cases as well as in patients with VD, showing a modest improvement in cognition, behavior, and function (Table 2); and (13) the effects of donepezil are dose-dependent, with optimal effects in the range of 5–10 mg/day.

After 20 years of experience in AD therapeutics, we can conclude that the main causes of therapeutic failure with AChEIs in general and donepezil in particular in AD are the following: (1) the central cholinergic deficit in AD is not the cause of the disease but the consequence of neurodegeneration associated with complex pathogenic mechanisms involving many different genomic, proteomic, and metabolomic cascades; (2) pharmacokinetic and pharmacodynamic weaknesses of the AChEIs; (3) an out-of-date screening protocol (outcome measures) to evaluate drug efficacy only relying on psychometric parameters, neglecting the fundamental utility of biological markers and/or predictors of neuroprotection in the long-term; (4) critical problems of patient recruitment not differentiating pure AD cases from cases of AD with cerebrovascular component and/or other medical conditions; (5) differences in the genetic profile of AD patients who exhibit a genotype-related therapeutic response (pharmacogenomics; efficacy issues); and (6) pharmacogenetic problems associ-

ated with genes responsible for the metabolism of drugs (pharmacogenetics; safety issues).

Despite all these considerations, AChEIs may be of some utility in 20%–30% of AD patients, and in this selected cluster of moderate responders the AChEIs should be used until other better therapeutic alternatives are available. The potential efficacy of donepezil in responders may be due to an adequate pharmacogenetic-pharmacogenomic profile associated with cholinesterase inhibition and/or other mechanisms of action directly or indirectly linked to cholinergic regulation (ie, anti-oxidation, inhibition of neuronal excitotoxicity-related mechanisms, cerebrovascular regulation).

Some other conclusions can also be drawn, such as that: (a) AChEIs (and most anti-dementia drugs) do not appear to be cost-effective; (b) novelty criteria and marketing pressure are not good advisers for treatment shift from a drug to another (there is no clear evidence that one AChEI is better than another, but some AChEIs are more harmful than others); (c) some pharmacological properties of donepezil might be beneficial in other forms of dementia and also in some other CNS disorders; (d) multifactorial interventions with combination therapy (including donepezil in the cocktail) may be more effective in AD than monotherapies; (e) in any circumstance, the therapeutic response in AD depends largely on the genomic profile of the patients; (f) cholinesterase inhibitors should be avoided in those AD patients in whom their genomic profile predict a poor therapeutic outcome; and (g) pharmacogenetics and pharmacogenomics studies can contribute to optimize therapeutics in the coming future by improving efficacy and safety and reducing costs.

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