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Cholinesterase Inhibitors in Dementia. Ten Years of Donepezil in Alzheimer's Disease and CNS Disorders (1996-2006): Therapeutic Assessment and Pharmacogenetics

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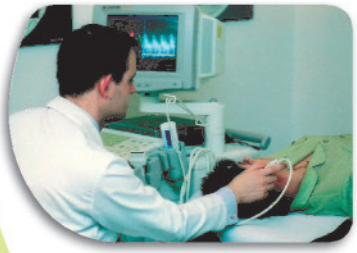

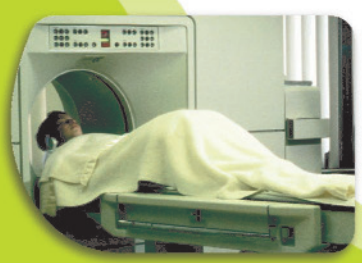

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CONTENTS

ABSTRACT

A decade after its approval by the FDA, 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 (2-3 points on ADAS-Cog vs placebo), responder rate (30-55%), dropout cases (20-40%) and side-effects (25-38%) in AD. Although donepezil represents a non cost-effective treatment, most studies convey that this drug can provide a modest benefit to cognition, behavior, and activities of the daily living in AD, contributing to slow-down disease progression and, to a lesser extent, delaying institutionalization. Some potential effects of donepezil on the AD brain, leading to reduce 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, inhibition of ß-amyloid aggregation and deposition, and indirect effects on cerebrovascular function improving brain perfusion.

Donepezil has also been used to treat other forms of dementia (vascular dementia, dementia with Lewy bodies, Parkinson dementia, progressive supranuclear palsy), and different CNS disorders (stroke, chronic amnesia, aphasia, migraine, Down's syndrome, Korsakoff's syndrome, post-traumatic brain injury, delirium, psychosis, bipolar disorder, tardive dyskinesia) with unclear results. Some clusters of patients with other dementia types might benefit from donepezil in a similar fashion to that of AD patients.

Recent studies demonstrate that the therapeutic response in Alzheimer's disease (AD) is genotype-specific. More than 200 genes are potentially associated with AD pathogenesis and neurodegeneration, and approximately 1,400 genes distributed across the human genome account for 20 to 95% of variability in drug disposition and pharmacodynamics. 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 cholinesterase inhibitors; about 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. 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 ultrarapid metabolizers (UM)(*1xN/*1)(8.04%). In addition, the presence of the APOE-4 allele in genetic clusters integrating CYP2D6 and APOE genotypes contributes to deteriorate the therapeutic outcome, and potential good responders can be converted into non-responders by the APOE-4/4 genotype among EMs and PMs. It is very likely that pharmacogenetic and pharmacogenomic factors account for 75-85% of the therapeutic response in AD patients treated with donepezil and other cholinesterase inhibitors metabolized via enzymes of the CYP family.

Key words

Donepezil, cholinesterase inhibitors, Alzheimer's disease, vascular dementia, CNS disorders, pharmacokinetics, pharmacodynamics, CYP2D6, APOE, pharmacogenetics.

INTRODUCTION

Donepezil is the number one member of the second generation of acetylcholinesterase inhibitors (AChEIs) (i.e., donepezil, rivastigmine, galantamine) (Table 1) developed for the treatment of Alzheimer's disease after the postulation in the early 1980s that AD was associated with a central cholinergic deficit (1,2). 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 (3,4). After the shut down of the tacrine business, donepezil became the new star of AD 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 CNS disorders. At the present time, donepezil is the leading compound for AD treatment in the world (marketed in 56 countries) (5). During the past decade, other types of dementia and different modalities of central nervous system (CNS) disorders have been experimentally treated with donepezil, showing unclear results (6).

Drugs approved by the FDA and other regulatory authorities in Europe and Japan for the treatment of Alzheimer's disease (AD) include the AChEIs tacrine, donepezil, rivastigmine, and galantamine (3,4-6,7) (Table 1), and the NMDA receptor partial antagonist memantine (8-11). Major issues for a drug to be successful include efficacy, safety, and at least some pharmacoeconomic benefit. In the case of AD, most anti-dementia drugs have been involved in controversy for years because of lack of efficacy (poor improvement in cognitive function and unclear evidence of effective neuroprotection), unsafe properties (adverse drug reactions, unpredictable effects of chronic treatments on neuronal survival), and doubtful cost-effectiveness (12-15). In the history of pharmacology, it has sometimes occurred, that a drug was introduced in the market not because of its scientific value or pharmacological benefit, but because there was nothing better. In the case of donepezil, the Ministry of Health of Japan, being the compound E2020 (donepezil) a Japanese patent of Eisai, was reluctant for more than 10 years to approve the new drug to be used in Japan until the advent of foreign pressures.

On average, most studies with AChEIs reported by the pharmaceutical industry showed a cognitive enhancement of 2-3 points (vs placebo) in the ADAS-Cog score in clinical trials of 12-30-week duration, with improvement in 12-58% of patients, 5-73% of drop-outs, and side effects in 2-58% of cases (4). 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%) (4). Most studies agree that donepezil is a safe drug, although important adverse drug reactions (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 (14-18). Concerning pharmacoeconomic aspects, some studies assessing the cost-effectiveness of AChEIs suggest that AChEI therapy provides benefits at every stage of disease, with better outcomes resulting from persistent, uninterrupted treatment (19-21), whereas other studies indicate that AChEIs are not cost-effective, with benefits below minimally relevant thresholds (14,15,22) or cost-neutral (23-25). Memantine shows benefits on cognitive and global function on the same order of magnitude as seen with AChEIs (9,20,26-28); however, a recent systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe AD concludes that memantine appears to be beneficial when assessed using functional and global measurements; in contrast, the effect of memantine on cognitive scores and behaviour and mood outcomes is less clear (29). 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 (12,13). 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$4,500-6,000 per year (˜US$50,000 in a decade) on medicines.

Since the past experience with AD therapeutics was clearly unsuccessful, donepezil is a good paradigm, as the most frequently prescribed drug to patients with dementia in the US (68%) (30), to interpret the past and to plan ahead future pharmacological challenges in order to optimize the treatment of dementia. In most European countries donenezil is also the most commonly prescribed drug, but less than 30% of the AD population is currently being treated with AChEIs (31; Cacabelos et al, unpublished results). Physicians in some countries are reluctant to prescribe AChEIs; in other countries, the prescription of AChEIs is restricted to some specialists; and in more than half of the cases the administration of AChEIs might not be justified. Furthermore, efficacy and safety issues in AChEIs therapy are associated with pharmacogenetic factors which are responsible for more than 50% of pharmacokinetic and pharmacodynamic properties of drugs.

ALZHEIMER'S DISEASE PATHOGENESIS AND POTENTIAL PHARMACOLOGICAL TREATMENTS

AD is a polygenic/multifactorial complex disorder characterized by the premature death of neurons. More than 200 different genes distributed across the human genome are potentially involved in the pathogenesis of AD (32). 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 (Aß) 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) (13,32-39). (b) multiple polymorphic variants of risk characterized in more than 200 different genes can increase neuronal vulnerability to premature death (13,32,33,38). 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 (32). APOE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD (32,36,37,40). (c) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity (41,42). 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 (32). 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 (12,13,32,43).

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 (e.g., nutrition, toxicity, social factors) (12,13,32,43,44). 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 (13,32).

Although the amyloid hypothesis is recognized as the *primum movens* of AD pathogenesis (32,34,35), 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. 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 (32,43). All these neurochemical events are potential targets for treatment; however, it is very unlikely that a single drug alone will be able to neutralize the complex mechanisms involved in neurodegeneration (12,13).

Modern therapeutic strategies in AD are addressed to interfere with the main pathogenic mechanisms potentially associated with AD (12,13). Major pathogenic events (drug targets) and their respective therapeutic alternatives include the following (Table 4): (i) genetic defects: gene therapy and RNAi; (ii) ß-amyloid deposition: ß-secretase inhibitors, γ-secretase inhibitors, α-secretase activators, Aß-fibrillation and aggregation inhibitors, amyloid immunotherapy (active and passive vaccination), copper chelating agents, solubilizers of Aß aggregates, APP production inhibitors, and Aß selective regulators (reticulons, chaperones); (iii) tau-related pathology: phosphatase activators, GSK-3 inhibitors, Cdk5 inhibitors, p38 inhibitors, JNK inhibitors; (iv) apoptosis: caspase inhibitors; (v) neurotransmitter deficits: acetylcholine enhancers (acetylcholine-release stimulants, acetylcholine reuptake inhibitors, cholinesterase inhibitors, choline-acetyl-transferase stimulants, muscarinic antagonists, nicotinic agonists), GABA modulators (inverse GABA-receptor agonists), glutamate modulators (NMDA antagonists, ampakines), dopamine reuptake inhibitors, adrenoreceptor modulators, histamine H3 antagonists, and serotonin modulators (5HT3 and 5HT1A receptor agonists, 5HT6 receptor antagonists, serotonin stimulants); (vi) neurotrophic deficits: neurotrophic factors, growth factors, synthetic neuropeptides, and natural compounds with neurotrophic activity; (vii) neuronal loss: neuronal stem cells, growth factors, neurite outgrowth activators, NOGO inhibitors, MOP inhibitors, GSK3 inhibitors, JNK inhibitors, and p38 inhibitors; (viii) neuroinflammation: COX1 and COX2 inhibitors, complement activation inhibitors, p38 inhibitors, eNOS inhibitors, PPAR α agonists, PPARγ agonists, novel NSAIDs, and cytokine inhibitors; (ix) oxidative stress: antioxidants, caspase inhibitors, and antioxidating enzyme enhancers; (x) calcium dysmetabolism: calcium channel blockers; (xi) neuronal hypometabolism: PPARγ agonists, and GSK3 inhibitors; (xii) lipid metabolism dysfunction: HMG-CoA reductase inhibitors, PPARγ agonists, and novel biomarine lipoproteins; (xiii) cerebrovascular dysfunction: vasoactive substances, NO inhibitors, HIF inhibitors, dandrolene-related agents, novel lipoproteins with anti-atherosclerotic activity, and liver X receptor agonists; (xiv) neuronal dysfunction associated with nutritional deficits: brain metabolism enhancers, nutrigenomic agents, and nutraceuticals; and (xv) a miscellany of pathogenic mechanisms potentially manageable with diverse classes of chemicals (10,12,13,35,45-56) (Table 4).

THE CHOLINERGIC HYPOTHESIS AND DONEPEZIL

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 due, in part, to a cholinergic deficit in the brain of affected people due to a loss of neurons in the basal forebrain, thus giving rise to the cholinergic hypothesis of AD (1,57). The role of acetylcholine on memory function had been postulated many years before (58), and it was reasonable to think that a cholinergic deficit

associated with an age-related decline in the number of neurons (50-87%) in 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 (2). 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 (32). 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 (32).

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, facilitating cholinergic neurotransmission (4). The first candidate to fulfil this criteria was tacrine (tetrahydroaminoacridine) (59), which after its introduction in the market in 1993 fell into disgrace 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 (4).

PHARMACOLOGICAL PROPERTIES

Donepezil, 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride (E2020), is an indanone benzylpiperidine derivative (60-62) with selective reversible AChEI activity in the CNS and other tissues (5,63,64). Donepezil is approximately 10 times more potent than tacrine as an inhibitor of acetylcholinesterase (AChE), and 500-1000-fold 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) (65). After extensive metabolization in the liver, the parent compound is 93% bound to plasma proteins (66).

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 (Table 5). Their chemical structures are also responsible for their pharmacokinetic and pharmacodynamic properties (67). 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-BuChE; and huperzine A is a pyridine with specific, reversible AChE inhibition (4). 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

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

Properties	Tacrine	Donepezil	Rivastigmine	Galantamine
Class	Aminoacridine	Piperidine	Carbamate	Tertiary alkaloid
AChE inhibition	Reversible Noncompetitive	Reversible Noncompetitive	Pseudo-irreversible Noncompetitive	Reversible Competitive
Dosis (mg/day)	80-160	5-10	6-12	16-24
Duration	Short-acting	Short-acting	Intermediate-acting	Short-acting
Brain AChE selectivity IC50 (nmol/L)	125	33	42,000	3,900
Serum BuChE selectivity IC50 (nmol/L)	7.2	988	54,000	18,600
BuChE/AChE selectivity	0.06	30	1.3	4.8
Cmax (ug/L)	5.1 (10 mg) 20.7 (20 mg) 33.9 (30 mg)	7.2 (5 mg) 25.6 (10 mg)	5.07 (2 mg x 2) 14.1 (6 mg x 2)	42 (12 mg x 2) 137 (16 mg x 2)
Tmax (hrs)	1-2	3-5	0.5-2	0.9-2
AUC (ug/L/h)	2-4	539	15.4 (3 mg x 2) 55.9 (6 mg x 2)	1.1
T1/2 (hrs)	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 Metabolism	CYP1A2 CYP2D6	CYP2D6 CYP3A4	Carbomoylation	CYP2D6 CYP3A4
Active Metabolites	1-Hydroxy-tacrine	6-O-Desmethyl Donepezil	NAP 226-90	Sanguinine
Urine excretion (%)	<3	17	Metabolite	50
Efficacy ADAS-Cog>Placebo	4.8	2.9	3.78	2.14
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

Source: R. Cacabelos, CIBE Database (2006); Cacabelos (12,13); Bentué-Ferrer et al (79); Giacobini (3,4).

TAK-147 showed high selectivity for AChE over BuChE; the carbamate derivatives showed moderate selectivity, while the 4-aminopyridine derivatives tacrine and ipidacrine showed no selectivity (68). 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 for 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 (69). Huperzine A, a novel alkaloid isolated from the Chinese herb Huperzia serrata, is a potent, highly specific and reversible inhibitor of AChE with better penetration through the blood-brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action than tacrine, donepezil and rivastigmine (70). Donepezil binds within the active site gorge of the protein to reversibly inhibit AChE activity in a fashion similar to the anticancer prodrug 7-ethyl-10-[4-(1-piperidino)-1-piperidino-]carbonyloxycamptothecin (CPT-11), a highly effective camptothecin analog that has been approved for the treatment of colon cancer (71).

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 may potentially 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 (72-78). 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%) (4,67,79-82). 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 (83). 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 faeces. 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) (78).

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 were 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 (84) and produces a dose-dependent increase in hippocampal theta rhythm amplitude elicited by stimulation of the brainstem reticular formation (85). AChE activity in human blood shows 60-97% and 43-89% of pre-exposed level after one and three days of donepezil administration at a daily dose of 5 mg, respectively (86). 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 (82).

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 (87) compared the effects of 8 AChEIs (tacrine, bis-tacrine, donepezil, rivastigmine, galantamine, heptyl-physostigmine, TAK-147, metrifonate) 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 (87).

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 (88).

Donepezil up-regulates nicotinic receptors in cortical neurons, this probably contributing to enhance neuroprotection (89). 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) (90). In the transgenic Tg2576 mouse model of AD, which exhibits age-dependent ß-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 (91). In AD cases, donepezil increases the percentage of REM (rapid eye movements) sleep to total sleep time, improving sleep efficiency and shortening sleep latency (92,93). In healthy volunteers, donepezil specifically enhanced the duration of REM sleep (% sleep period time) and the number of REMs (94). 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 (95).

The influence of AChEIs on APP processing and inhibition of ß-amyloid formation, at least in the case of some AChEIs (e.g., 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-ß responsive element which has been proposed as a target for drug development (96). Donepezil and other AChE noncovalent inhibitors are able to inhibit AChE-induced ß-amyloid aggregation (97). AChEIs may also protect against vascular damage and amyloid angiopathy. In AD patients, increased levels of markers of endo-

Table 2. Selected studies with donepezil in dementia.

Author	Year	Disease	N	Study	Effect	Outcome Measures	Comments
Rogers et al (115)	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 (116)	1998	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 (117)	1998	mAD	473	Double-blind Placebo-controlled	Positive (24 w)	ADAS-Cog; CDR-SB; CIBIC+; MMSE; QoL	25% responders 22% Dropout No changes in QoL
Shea et al (284)	1998	DLB	9	Open-label	Positive (12 w)	Cognition, hallucinations, parkinsonism, functional abilities	Improvement in cognition and hallucination and worsening of parkinsonism
Burns et al (118)	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 (386)	2000	mAD	133	Double-blind Placebo-controlled	Positive (254 w)	ADAS-Cog; CDR-SB	Safety
Matthews et al (232)	2000	mAD	80	Open-label	Positive (18 m)	ADAS-Cog; MMSE; NPI	Cognitive and behavioral improvements in 39% and 37% of patients, respectively
Greenberg et al (387)	2000	mAD	60	Double-blind Placebo-controlled Crossover	Positive (6 w)	ADAS-Cog	Modest improvement
Homma et al (119)	2000	mAD	263	Double-blind Placebo-controlled	Positive (24 w)	ADAS-Jcog; CDR-SB; CMCS; J-CGIC; MENFIS	28% Responders 14% Dropout 10% AEs
Samuel et al (285)	2000	DLB	16	Open-label	Positive (6 m)	MMSE; BEHAVE-AD; EMG; EPS	Cognitive and behavioural improvement
Lanctôt and Herrmann (16)	2000	DLB	7	Open-label	Positive (8 w)	MMSE; NPI;	Mild improvement in cognition and behaviour
Winblad et al (120)	2001	mAD	286	Double-blind Placebo-controlled	Positive (52 w)	ADL; GBS; GDS; MMSE; NPI	33% Dropout Modest improvement
Mohs et al (121)	2001	mAD	431	Double-blind Placebo-controlled	Positive (52 w)	ADFACS; CDR-SB; MMSE	74% Dropout 51% responders
Feldman et al (123)	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 (198)	2001	m/sAD AD+CVD	208	Double-blind Placebo-controlled	Neutral (24w)	MMSE; NPI-NH; CDR-SB; PSMS	82% completed the study; 97% AEs; concomitant medications; comorbidity; institutionalized patients; cognitive stabilization
Doody et al (184)	2001	AD	763	Double-blind Placebo-controlled	Positive (24 w)	MMSE; ADAS-Cog; CDR-SB	Cognitive improvement
Doody et al (7)	2001	mAD	205	Follow-up	Positive (1 y)	MMSE	Slower decline in MMSE scores
Litvan et al (303)	2001	PSP	21	Double-blind Placebo-controlled	Negative (6 w)	Cognition, function, ADL Double Memory Test	ADL and motor function worsening; Mild improvement in cognition
Fabbrini et al (304)	2001	PSP	6	Open-label	Negative (3 m)	Cognition; ADL	No effect
Parnetti et al (156)	2002	AD	59	Placebo-conrolled	Positive (6 m)	CSF AChE activity, BuChE activity; β-amyloid, tau, phosphrylated tau proteins	Decrease in AChE activity, and no changes in other biomarkers
Paleacu et al (233)	2002	mAD	28	Open-label	Positive (6 m)	MMSE; NPI	Significant improvement in behavioural symptoms
Nobili et al (268)	2002b	mAD	25	Open-label	Positive (1 y)	SPECT (brain perfusion)	Preserved brain perfusion
Frolich et al (495)	2002	AD+CVD	913	Open-label	Positive (3 m)	MMSE; QoL	Improvement in MMSE and QoL; All patients (AD+CVD) were previously treated with several nootropics;
Gauthier et al (235)	2002	m/sAD	290	Placebo-controlled Randomized	Positive (24 w)	NPI	Improvement in behavioural symptoms
Gauthier et al (234)	2002	mAD	207	Double-blind Placebo-controlled	Positive (24 w)	CIBIC+	Cognitive and functional improvement; 82% of patients showed adverse events
Wilkinson et al (210)	2002	mAD	111	Open-label Comparative: vs rivastigmine	Positive (12 w)	ADAS-Cog	Similar improvement; less side-effects; Better compliance with donepezil
Krishnan et al (153)	2003	mAD	67	Double-blind Placebo-controlled	Positive (24 w)	Cognition; MRI	Cognitive improvement and decrease in hipocampal atrophy

Kemp et al (155)	2003	mAD	12	Double-blind Placebo-controlled	Positive (4 m)	ADAS-Cog; SPECT-M1 muscarinic receptor binding	Cognitive improvement and increase M1 binding
Wilcock et al (222)	2003	mAD	182	Rater-blinded Comparative	Negative (52 w)	MMSE; BrADL; ADAS -Cog; NPI; SCB	Galantamine better than donepezil
Black et al (254)	2003	VD	603	Placebo-controlled Randomized	Positive (24 w)	ADAS-Cog; CIBIC-Plus; ADFACS; CDR-SB	Improvement in cognition, function and ADL
Wilkinson et al (255)	2003	VD	616	Placebo-controlled Randomized	Positive (24 w)	ADAS-Cog; CIBIC+	Improvement in cognition and global function
Feldman et al (134)	2003	m/sAD	290	Double-blind Placebo-controlled Randomized	Positive (24 w)	DAD; IADL+; PSMS+	Slower cognitive decline and better ADL performance
Minett et al (410)	2003	DLB PDD	19	Open-label Discontinuation	Positive (20 w)	MMSE; NPI	Worsening after donepezil withdrawal
Adunsky et al (408)	2004	AD	105	Open-label	Negative	Plasma lipid profile	Increased levels of cholesterol, triglycerides, LDL and V LDL in donepezil users
Salloway et al (180)	2004	MCI	270	Double-blind Placebo-controlled	Neutral (24w)	NYUPDRT; ADCS CGIC -MCI; ADAS-Cog; PGA	20% dropout; 88% adverse events (73% placebo)
Nadeau et al (274)	2004	Stroke	20	Exploratory randomized, double-blind, placebo-controlled, parallel group study	Positive	Wolf Motor Function Test Motor Activity Log Box and Block Test Actual Amount of Use Test Fugl-Meyer Motor Scale-Upper Extremity Caregiver Strain Index	Only positive for WMFT
Holmes et al (236)	2004	mAD	134	Randomized withdrawal	Positive (6 w)	NPI	Improvement in neuropsychiatric symptoms
Tariot et al (196)	2004	m/sAD	404	Combination therapy: donepezil + memantine	Positive (6 m)	MMSE; ADCS-ADL; SIB; CIBIC+; NPI; BRSGP	Improved cognition, ADLs, global function, behaviour and care dependence
Froelich et al (496)	2004	mAD	237	Open-label	Positive (24 w)	MMSE	Cognitive improvement; 80% responders; Alterations in ECG parameters
Beusterien et al (214)	2004	mAD	3864	Retrospective	Positive (>1yr)	Nursing Home Placement (NHP)	4.4% vs 11.0% in controls
Seltzer et al (133)	2004	mAD	96	Double-blind Placebo-controlled	Positive (24w)	ADAS-Cog; MMSE; CMBT; CDR -SB; PGAS; AS	Early-stage AD
Courtney et al AD2000 Collaborative Group 2004 (22)	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 (221)	2004	mAD	64	Open-label Comparative: donepezil vs galantamine	Positive (12 w)	ADAS-Cog; MMSE; DAD Satisfaction rate	Donepezil superior to galantamine
Finkel et al (205)	2004	mAD	120	Placebo-controlled Randomized	Neutral (12 w)	NPI; CGI; CGI-S	Neutral effect of the combination therapy
Thomas et al (271)	2005	VD/AD	16/ 15	Open-label	Positive (16w)	MMSE; working memory tests; delayed recognition memory	Marginal effects on MMSE score Gains in working memory
Bartorelli et al (419)	2005	mAD	225	Observational Switching from donepezil to rivastigmine	Positive (3 m)	MMSE; ADL; IADL; CGIC	Improvement in cognitive function after switching (>60% responders)
Gasper et al (160)	2005	SD	5423	Observational	Positive	Mortality Rate in nursing home residents in 6 US States (N=915,469)	Reduced mortality rate
Hashimoto et al (149)	2005	mAD	54	Open-label	Positive (1 yr)	MRI; Mean annual rate of hippocampal volume loss	Control subjects have never been under AChEI treatment
Bragin et al (195)	2005	mDD	35	Open-label Combination therapy	Positive (1 y)	Global evaluation	Combination of antidepressants + AChEIs + supplements
Klinger et al (421)	2005	mAD	913	Post-Marketing Surveillance	Positive (3m)	MMSE, QoL	Observational PMS study in patients previously treated with memantine or nootropics
Bullock et al (124,186)	2005	m/sAD	994	Double-blind Comparative	Neutral	Cognitive function; activities of daily living; global functioning; behavioural symptoms	Comparative study: donepezil vs rivastigmine; Better results with rivastigmine in carriers of the wild-type BuChE genotype
Bizzarro et al (461)	2005	mAD	41	Observational	Negative (1 yr)	MMSE; APOE	No cognitive improvement; APOE-related responses
Roman et al (260)	2005	VD	1219	Double-blind Placebo-controlled	Positive (24w)	ADAS-Cog; MMSE; CIBIC+; CDR -SB; ADFACS; ADFACS -IADL	Combined analysis of 2 large-scale trials in 109 investigational sites in USA, Europe, Canada and Australia
Petersen et al (175)	2005	MCI	769	Double-blind	Negative (3 yrs) Positive (1 yr)	Conversion to AD; cognition; function	Comparative with vitamin E; Positive results in APOE-4 carriers

Ancoli-Israel et al (223)	2005	mAD Sleep disorder	63	Double-blind Placebo-controlled	Neutral (8 w)	Actigraphy	No effect on sleep; Comparative: donepezil vs galantamine
Feldman et al (136)	2005	m/sAD	290	Placebo-controlled Subgroup analysis	Positive	CIBIC+; MMSE; SIB; NPI; DAD	Benefits over placebo on global, cognitive, functional, and behavioral measures
Thomas et al (298)	2005	PDD DLB	70	Open label	Positive (20w)	MMSE; NPI; UPDRS-III	69% side-effects; similar results in PDD and DLB (cognition, behaviour); no improvement in psychomotor function
Winblad et al (125)	2006	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 (388)	2006	mAD	619	Open-label 12-24w Double-blind Placebo-controlled 12w Single-blind 12w	Positive (12-24w)	ADAS; MMSE; DAD; NPI	69% Responders 31% Non-responders Cognitive and behavioural benefit
Bullock et al (213)	2006	mAD	994	Randomized	Partial effects (2 yrs)	SIB; NPI; GDS; MMSE; ADCS-ADL	Age-dependent response BuChE genotype-related response
Paci et al (270)	2006	VD	10	Open-label	Positive (1 m)	Cognition; P300 ERP	Improvement in P300 latency
Winblad et al (126)	2006	m/sAD	286	Open-label	Positive (3 yrs)	MMSE; GBSS; GDS; NPI	Delayed progression of disease; 90% ADRs
Shimizu et al (154)	2006	mAD	51	Open-label	Neutral (10-14 m)	MMSE; SPECT (rCBF)	Improvement in frontal rCBF
Touchon et al (215)	2006	AD-DLB	94	Retrospective Comparative: donepezil 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 (197)	2006	m/sAD	404	Combination therapy with memantine	Neutral (24 w)	ADCS-ADL; SIB; CIBIC+; NPI	Improvement and stabilization of symptoms
Mori et al (288)	2006	LBD	12	Open-label	Positive (12w)	NPI; ADAS-Jcog; UPDRS	Plateau effect at 4w

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 Cargiver 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: Gottfries-Brane-Steen 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: Intent-to-treat last observation carried forward
J-CGIC: Japanese version of CGIC
mAD: mild-moderate Alzheimer's disease
MCI: mild cognitive impairment
mDD: Mild dementia and depression
MENFIS: Mental Function Impairment Scale
MMSE: Mini-Mental Status Examination
NPI: Neuropsychiatric Inventory
NPI-NH: Neuropsychiatric Inventory-Nursing Home Version
NYUPDRT: New York University Paragraph Delayed Recall test
QoL: Quality of Life
PDD: Parkinson's disease with dementia
PDS: Progressive Deterioration Scale
PGAS: Patient Global Assessment Scale
PSMS+: Modified Physical Self Maintenance Scale
PSP: Progressive supranuclear palsy
sAD: moderate-severe Alzheimer's disease
SD: Senile Dementia
SIB: Severe Impairment Battery
UPDRS-III: Unified Parkinson's Disease Rating Scale
VD: Vascular Dementia

thelial dysfunction, such as thrombomodulin and sE-selectin have been observed. After treatment with AChEIs for one month, the levels of both parameters are markedly reduced, with values approaching normal ranges (98). 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 (99). In contrast, donepezil protects against the neurotoxic effects induced by ß-amyloid(1-40) in primary cultures of rat septal neurons (100). In another transgenic model of AD, the AD11 anti-nerve growth factor (anti-NGF) mice, oral administration of ganstigmine (CHF2819) and donepezil reversed the cholinergic and behavioural deficit in AD11 mice but not the amyloid and phosphotau accumulation, uncovering different mechanisms leading to neurodegeneration in AD11 mice (101).

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 (102). The enhancement of the somatotropinergic system (GRF-GH-IGF) associated with donepezil treatment might contribute to activate GRF/GH-related neurotrophic mechanisms leading to neuroprotection and cognitive improvement (103,104). AChEIs also influence pro-inflammatory cytokines released from peripheral blood mononuclear cells, increasing oncostatin M, IL-1ß, and IL-6 levels in AD patients after treatment (105).

Glutamate-related excitotoxicity is an additional deleterious mechanism secondarily contributing to AD neuropathology (11). 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 (106). 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 (107). Other studies indicate that donepezil has a neuroprotective effect against oxygene-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 (108).

Donepezil influences cell 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 (109). 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 $\alpha 7$ nicotinic receptors and the PI3K-Akt pathway (110). In addition, donepezil increases action potential-dependent dopamine release (111) and modulates nicotinic receptors of substantia nigra dopaminergic neurons (112).

To show positive effects in experimental animals, AChEIs should be given before the trial. Different AChEIs exhibit differential effects on cognition in animal models, and their effect on cognition appears to derive from the improvement of processes of acquisition of object information, in contrast to the effect of phosphodiesterase type 5 inhibitors (PDE5) which improve processes of consolidation of object information (113). There is also preliminary evidence in AD that the aspect of memory that is most affected by AChEIs appears to be facilitation of retention of new information in memory (114).

DONEPEZIL IN ALZHEIMER'S DISEASE

Most clinical trials with donepezil in Alzheimer's disease during the past 10 years have been performed in patients with mild-to-moderate dementia (mAD) (115-122) (Table 2), and a small number of studies has been carried out in severe cases of AD (sAD) (123-125) (Table 2). More than 10,000 patients recruited from 26 different countries have been included in major clinical trials with AChEIs (24-30 week-duration) during the past 10 years (4). The typical outcome measure in most trials is cognitive performance as assessed with the ADAS-Cog and/or MMSE scales. In other studies, the psychometric assessment of cognition, behavior and function is the principal outcome measure. In untreated patients the estimated cognitive decline is equivalent to 8 points in the ADAS-Cog scale. 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 (4,126). Despite this optimistic view resulting from the observation of selected trials (Table 2), many other studies and meta-analyses (14-18,127-130) 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 the 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% (16). 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 (16). 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 (18). In a 10-study meta-analysis of donepezil in AD and two-study combined analysis of donepezil in vascular dementia (VD), an Irish group concludes 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 (131). In the AD2000 clinical trial of Courtney et al (22), 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 behavioural and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil (22). 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 (132) 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 (132).

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 (133). 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 favour of a positive therapeutic intervention with donepezil in sAD (123-125,134-136). In the international literature there are 13 articles related to donepezil in sAD, but only 3 fulfil strict criteria for further consideration (137).

In one study to evaluate efficacy and safety of donepezil in sAD, Feldman et al (123) found that donepezil had significant benefits over placebo on global, cognitive, functional, and behavioural measures in patients with sAD (123,136). In another study by Feldman et al (134), donepezil demonstrated a significantly slower decline than placebo in instrumental and basic ADLs in patients with m/sAD. Bullock et al (124) found similar effects of donepezil and rivastigmine on cognition and behaviour in m/sAD. Winblad et al (125) 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 changes 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 were assigned donepezil and 99 patients were assigned placebo 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 (125).

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 (138) studied a cohort of older adults newly dispensed donepezil (N=6,424) 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 (138).

Despite conventional measures of cognitive function, it has been hypothesized that cognitive-communication stimulation in combination with donepezil would positively affect relevance of discourse, performance of functional abilities, emotional symptoms, quality of life, and overall global function, as measured by caregiver and participant report and standardized measures (139).

It would be highly recommendable that outcome measures of efficacy in the long-term incorporate specific AD-related biologic markers (e.g., serum markers, CSF markers, neuroimaging biomarkers (MRI, fMRI, PET, SPECT), brain atrophy rate, brain perfusion, optical topography, etc) (140-142). 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 (143). The degree of cortical AChE inhibition correlates with changes in executive and attentional functions (144). Long-term treatment with donepezil can lead to a lesser deterioration in qEEG, paralleling a milder neuropsychological decline (145), with reduction of slow-wave activity in frontal and temporo-parietal areas (146). Short-term studies showed contradictory qEEG results in AD (147). Mean P300-related evoked potentials are also improved in dementia after donepezil treatment (148). By using the rate of hippocampal atrophy as a surrogate marker of disease progression, Hashimoto et al (149) 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 (150). 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 (151). Atrophy of the substantia innominata was more pronounced in transiently and continuously responding groups than 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 (152). Krishnan et al (153) 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 (154). Furthermore, there is a parallelism between cognitive improvement and increase in brain M1 muscarinic receptor binding after treatment with donepezil in AD (155). AChE activity also decreases in the cerebrospinal fluid (CSF) of patients treated with donepezil, but changes in other biomarkers, such as BuChE activity, ß-amyloid(1-42), tau and phosphorylated tau proteins are not affected by donepezil treatment (156).

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 (157). Over 770 million days of patient use and an extensive publication database demonstrate that donepezil has a good tolerability and safety profile (158). 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 on 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 (159) stated (on a systematic 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 behaviour. Study clinicians rated global clinical state more positively in treated patients, and measured less decline in measures of global disease severity (128). In general terms, there is not robust support for any AChEI because the treatment effects are small and are not always apparent in practice (128,159). Donepezil treatment may be associated with reduce mortality in nursing home residents with dementia (160) and with delayed nursing home placement (161), although some authors denied that donepezil was able to reduce the rate of institutionalization or disability in mAD (22,162). 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 (163).

Cost-effectiveness analyses suggest that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of £80,000, with donepezil treatment reducing the mean time spent in full-time care by 1.42-1.59 months over a 5-year period due to its potential effect in delaying AD progression; cost saving associated with this reduction do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels acceptable for public health policy makers (British NHS) (15,164). In contrast, Americans estimate that donepezil therapy prescribed in routine clinical practice is associated with reduced health care costs to the Medicare managed care plan. The mean costs of medical services per year in the donepezil group studied by Lu et al (165) were US$2500 ($300-4671) less than those in the control group (p=0.024). Lower medical costs in the donepezil group ($3325; p<0.003 vs controls) were largely attributable to the lower costs of services performed in the hospital ($2594, p<0.004) and post-acute skilled nursing facility (SNF) ($1012; 0.001), which were partially offset by $1241 in higher prescription, physician's office, and outpatient hospital costs. Patients receiving donepezil had shorter mean lengths of stay in the hospital (3.00 vs 5.43 days; p<0.008) and post-acute SNF (0.42 vs 3.40 days; p<0.001) but a higher mean number of physician's office visits (10.91 vs 7.91 visits; p<0.001) (165). Usually, there are great differences among pharmacoeconomic studies between American (165-169) and European authors (14,15,23,24,164,170); in general, most European studies tend to demonstrate that donepezil in AD is cost-neutral or cost-ineffective (15,23,24,164,170,171).In Canada, although there is uncer-

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

ADRs	Frequency*	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
Haematic 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
Diarrhoea	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%	In combination with sertraline
Dyskinetic disorders	<1%	AD
Pancreatitis	<1%	AD
Seizures	1-3%	AD
Purpuric rash	<1%	AD
Prolonged effects of anaesthesia	<1%	AD

*Estimated values from clinical trials and clinical observations reported in the international literature (N=112)

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

tainty in estimated results and the differences emerging from meta-analyses are relatively small, the best information currently available suggested that the first choice for treatment of AD should be galantamine (172). In another Canadian study with m/sAD, after adjusting for baseline total cost per patient, the mean total societal cost per patient for the 24-week period was US$6,686 (Can 9,904 dollars) for donepezil and US$6,910 (Can 10,236 dollars) for placebo. This net cost saving of US$224 (Can 332 dollars) included the average 24-week cost of donepezil treatment. According to the Canadian authors, most of the cost-saving with donepezil treatment was due to less use of residential care by patients, and caregivers spending less time assisting patients with ADL (173).

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is the postulated transitional state between the cognitive changes of normal aging and early AD (174-176). The prevalence of MCI in the general population (>65 years of age) ranges from 3% to 19%. The amnestic subtype of MCI might represent a risk for AD (176). The rate of progression to clinically diagnosable AD is 10-15%/year among persons who meet the criteria for the amnestic form of MCI, in contrast to a rate of 1-2%/year among normal elderly persons (174,176). 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. It is very likely that AD neurons begin their deceasing process 20-40 years prior to the appearance of the first symptoms (e.g., memory deficit, behavioural 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 (13,33). 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 (176-178).

Few studies have been performed with donepezil in MCI (179). In a double-blind, placebo-controlled, multi-center trial in US with 270 cases, a mild benefit in cognitive function has been reported (180,181). A Chinese group has performed a clinical trial with donepezil (2.5 mg/day for 3 months) in patients with amnestic MCI and found a significant improvement in cognitive performance as well as changes in the hippocampus as assessed by magnetic resonance spectroscopy (MRS), suggesting that donepezil might induce astrocyte activation and improvement in interneuron connectivity (182).

In a recent study, Petersen et al (175) evaluated 769 subjects with the amnestic 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 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 (175).

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 (179). 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 (183). If the rate of conversion from MCI into AD is about 10-15%/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 (4,7,184-186) were never clearly documented in well-controlled trials. In a recent study, Winblad et al (187) 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 favour of continuous donepezil therapy (187).

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 (188)- 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 (188). 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 (8,9,33,188). The study of Petersen et al (175) 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 (e.g., galantamine) may even increase mortality (189,190).

Combination Therapies

Combination drug therapy is the standard of care for treating many neuropsychiatric disorders and other medical conditions (e.g., cardiovascular disease, hypertension, cancer, AIDS, diabetes, etc). 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 in different clinical settings (191). Multifactorial therapy combining several types of drugs with potential neuroprotective effect on the CNS have been tried in AD and other forms of dementia with promising results (10,12,13,188,192-194). Donepezil has been given in combination with other substances to patients with AD (195) and also to subjects with different CNS disorders. Probably the best evidence-based combination strategy is the addition of memantine to stable donepezil therapy in m/sAD (196,197). This combination was found to benefit cognition, behaviour, and activities of daily living. It appears that memantine in combination with donepezil is significantly better than donepezil alone in the management of behavioural symptoms (185,196,198,199). 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 (200). 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 (201) and memantine acts as a partial NMDA antagonist (11).

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 pharmacokinamics of donepezil, indicating that ginkgo supplementation does not have major impact on donepezil therapy (202). 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) (203). Initial data resulting from combination studies of donepezil and vitamin E indicated that this long-term combination might be beneficial for AD (204).

Donepezil + 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 behavioural and psychological symptoms (205). 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 (206). In some cases the combination of donepezil and neuroleptics may exacerbate extrapyramidal side-effects (207).

In general, combination therapy (AChEIs, neuroprotectants, nootropics, vasoactive substances, supplementation of vitamins and metabolic factors, nutraceuticals) tends to show better results than monotherapy with one AChEI or any other single drug for dementia (12,13,188). Similar results can be seen in animal models when donepezil is given in combination with other compounds (208). In animal models of memory impairment, co-administration of donepezil and selegiline -a monoamine oxidase-B inhibitor reported to improve cognitive function in dementia- at doses that do not show efficacy individually, significantly ameliorate scopolamine + p-chlorophenylalanine-induced memory deficits in rats studied in the Morris water maze (209).

Multifactorial Therapy

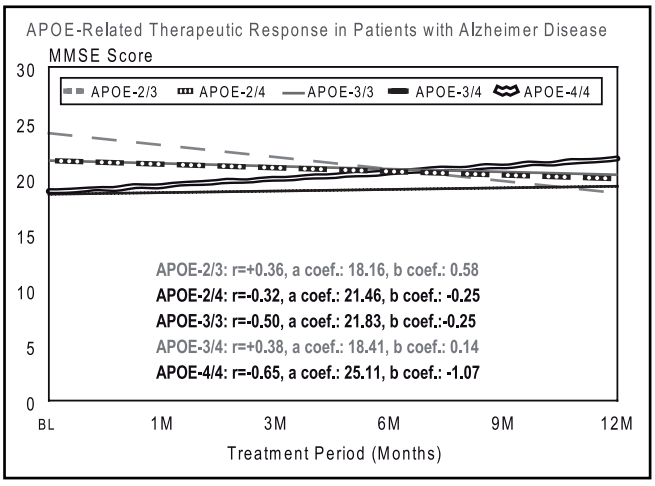


Figure 1. **APOE-Related therapeutic response in patients with Alzheimer's disease. Adapted from Cacabelos et al (188)**

Comparative Studies

Comparative studies with different AChEIs did not show any significant difference or traces of superiority among them in AD patients (124,157,210-212). 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 (4) 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%) (4).

In the study of Bullock et al (124) with 994 patients, donepezil and rivastigmine showed similar effects on cognition and behaviour. Only 57.9% of patients completed the study mainly due to adverse events, which were more frequent in the rivastigmine group during the titration phase, but similar in the maintenance phase. Serious adverse events were reported by 31.7% of rivastigmine- and 32.5% of donepezil-treated patients, respectively. AD patients who had genotypes that encoded for full expression of the butyrylcholinesterase enzyme (BuChE wt/wt; N=226/340), who were below 75 years of age (N=49/994) showed significant greater benefits from rivastigmine treatment (124). Age, genotype, and concomitant medical conditions can influence the differential response to AChEIs. Rivastigmine provides significant benefits in younger patients compared with donepezil on the NPI-10, NPI-12,

Table 4. Pathogenesis-related therapeutic strategies in Alzheimer disease and dementia

Pathogenic Mechanism	Therapeutic Strategy	Drug	Company
Genetic factors	Gene therapy		
Single gene-related	NGF gene therapy	Ceregene	Cell Genesys
Polygenic-related	RNAi		
β-amyloid deposition	β-secretase inhibitors	OM-99-2	Univ. Illinois & Oklahoma
		KMI-008	Kyoto
		Fs(OMOO-3)dR9	Oklahoma/Tokyo/Zapaq
		Hisidin	Kyungpook Natl Univ
		WO 0399202	Merck Sharp & Dohme
		WO 0302122	Elan/Pfizer
		WO 0345913	GlaxoSmithKline
		WO 0402483	Actelion
		US 6562783	NeuroLogic
	γ-secretase inhibitors	BMS	Bristol-Myers Squibb
		LY-411575	Lilly/Athena
		WEP-III-31C	Brigham/Harvard Med Sch
		WO 0393264	Merck Sharp & Dohme
		WO 0314095	Sanofi-Synthélabo
		WO 0359335	Bayer
		WO 366592	Pharmacopeia/Schring-Plough
	α-secretase activators		
	Aβ-fibrillization and aggregation inhibitors	PTI-00703	ProteoTech
		PPI-1019/APAN	Praecis
		NC-531	Neurochem
		β-Sheet breaker protein	Serono
		RS-0406	BTG/Sankyo
		Oxigon	Mindset BioPharmaceuticals
	Amyloid Immunotherapy	HF-0420	Hunter-Fleming
		AN-1792	Elan/Wyeth
		AAB-001 (hMAb)	Elan/Wyeth
		AAC-001	Elan/Wyeth
		Aβ synthetic homologues	Mindset BioPharmaceuticals
		Aβ Immunoconjugates	Neurochem/Praecis
		Aβ/High ordered config	Cytos/Novartis
		AAV-CB-Aβ42	Peking Union Med Col
	Copper chelating agents	MAbs	Merck & Co/Acumen
	Solubilizers of Aβ aggregates	Clioquinol/PBT-1	Prana
		DP-109	D-Pharm
	APP Production inhibitors	PBT-2	Prana
		Phenserine tartrate	Axonyx
	Aβ selective regulators	Posiphen	Axonyx/NIH
		Reticulons	
		Chaperones/SLF-CR	Howard Hughes Med Inst
Tau pathology	Phosphatase activators		
	GSK-3 inhibitors		
	Cdk5 inhibitors		
	P38 inhibitors		
	JNK inhibitors		
Apoptosis	Caspase inhibitors		
	Neurotrophic agents		
Neurotransmission deficits			
Acetylcholine	Acetylcholine-release stimulant	Montirelin	Nippon Seiyaku
		T-588	Toyama
		Dexefaroxan/RX-821037	bioMerieux-Pierre Fabre
	Acetylcholine reuptake inhibitor	MKC-231	Mitsubishi
Enzymes	Cholinesterase inhibitors	Tacrine	First Horizon/OTL Pharma
		Donepezil	Eisai/Pfizer
		Rivastigmine	Novartis
		Galantamine	Johnson &Johnson/Shire
		Metrifonate	Bayer
		7-Methoxytacrine	Res. Inst. Pharm. Biochem.
		Zanapezil/TAK-147	Takeda
		Ensaculin/KA-672	Schwabe
		Phenserine	Axonyx
		Ganstigmine/CHF-2819	Chiesi
		P-11149	Aventis
		NIK-247	Nikken
		Methanosulfonyl fluoride	Texas University
		T-82	SSP/Arena/Seiyaku
		Teserstigmine/CHF-2060	Chiesi
		ZT-1	Jiangsu Yangtse
	Choline-acetyl-transferase stimulant	Nefiracetam	Dai-ichi
Muscarinic receptors	Muscarinic agonists	Cevimeline/AF-102A	Dai-ichi/Nippon Kayaku
		PD-151832	Pfizer

	Muscarinic antagonists	Sch-211803	Schering-Plough
Nicotinic receptors	Nicotinic agonists	SIB-1553A	Merck
GABA	GABA modulators	Fasoracetam	Nippon Seiyaku
	Inverse GABA-receptor agonist	NDG-97-1	Neurogen/Pfizer
		S-8510	Shionogi/GlaxoSmithKline
Glutamate	Glutamate agonists	S-189861	Servier
NMDA	NMDA antagonists	Memantine	Merz/Lundbeck/Forest
AMPA	Ampakines	CX-516	Cortex/Servier
		Ampalex/CX-516	Cortex/Servier
		CX-691	Cortex/Servier
Dopamine	Dopamine reuptake inhibitors	NS-2330	Neurosearch/Boehringer
Noradrenaline	Adrenoreceptor modulators	Nicergoline	Pharmacia
Histamine	Histamine H3 antagonists	Cipralisant	Gliatec/Merck
Serotonin	5HT3 receptor agonist	T82	SSP/Arena
	5HT1A receptor agonist	Xaliproden/SR-57746A	Sanifi-Synthelabo
	Serotonin stimulant	FK-960	Fujisawa
Neurotrophic deficit	Neurotrophic agents	Cerebrolysin	Ebewe/Abbot
	NGF agonists	Xaliproden/SR-57746A	Sanofi-Synthelabo
	Growth factors	Ceregene	Cell Genesys
	Synthetic neuropeptides		
Neuronal loss	Neuronal stem cells		
	Growth factors		
	Neurite outgrowth activators		
	Synaptogenesis activators		
	Nogo inhibitors		
	MOP inhibitors		
	GSK-3 inhibitors		
	JNK inhibitors		
	P38 inhibitors		
Neuroinflammation	Cyclooxygenase-1 inhibitors	Naproxen	NIA/John Hopkins
	Cyclooxygenase-2 inhibitors	Celecoxib	Pfizer
		Rofecoxib	Merck
	Complement activation inhibitors		
	P38 inhibitors		
	Caspase-1 inhibitors		
	eNOS inhibitors	Argisat	eNOS Pharmaceuticals
	PPARα agonists		
	PPARγ agonists		
	Novel NSAIDs	Flurizan/R-Flurbiprofen	Myriad
	Cytokine inhibitors	Interferon-α_{2A}	NCRR
Oxidative stress	Antioxidants	Vitamine E	NIA/NCI
	Caspase inhibitors		
	Antioxidating enzyme enhancers		
Excitotoxic reactions	NMDA antagonists		
	Ampakines		
	Modulators of glutamate transporters		
Calcium dysmetabolism	Calcium channel blockers		
Neuronal hypometabolism	PPARγ agonists		
	GSK-3 inhibitors		
Lipid dysfunction	HMG-CoA reductase inhibitors	Atorvastatin	Pfizer/Yamanouchi
		Lovastatin/ADX-159	Andrx
	PPARγ agonists		
	Novel lipoproteins	E-SAR-94010	Ebiotec
		E-JUR-94013	Ebiotec
		E-CAB-94011	Ebiotec
Cerebrovascular dysfunction	Vasoactive substances	Nicergoline	
	NO inhibitors		
	HIF inhibitors		
	Dandrolene-related agents		
	Novel lipoproteins	E-SAR-94010	Ebiotec
	Liver X receptor agonists		
Neuronal dysfunction associated with nutritional deficiency	Nutrigenomics		
	Nutraceuticals	E-SAR-94010	Ebiotec
		E-JUR-94013	Ebiotec
		E-CAB-94011	Ebiotec
	Brain metabolic enhancers	Nutritional BME	NIA/Burke Med. Res. Inst.
Other pathogenic mechanisms	Estrogen agonists	ABPI-124	Mitokor/AHP
	Estrogen replacement	Estrogen	NIA/NCRR/AA
	Brain-targeted	Estrogen	Ivax
	Dabelotine/S-12024	Vasopressin modulator	Servier
	MAO-B inhibitors	Rasagiline	Lundbeck/TEVA
		SL-251188	Sanofi-Synthelabo
	Somatostatin stimulant	FK-960	Fujisawa
	Insulin sensitizer	Avandia/Rosiglitazone	VA Medical Res. Services
	Anti-inflammatory agents	Cyclophosphamide	NIMH
	Immunostimulants	Colostrinin	ReGen Therapeutics

	MAP kinase inhibitors	CEP-1347	Cephalon/Lundbeck
		CPI-1189	Centaur
	Muscarinic M1-receptor density	P-58	Phytopharm
	Choline uptake enhancer	MKC-231	Mitsubishi
	Prolyl-endopeptidase inhibitors	Z-321	Zeria
	Anti-neurodegenerative agents	SR-57667	Sanofi-Synthelabo
	Immunotrophins	Anapsos	Alacan/ASAC Pharma
	Endogenous nucleotides	CDP-Choline	Takeda, Ferrer
	Antibiotics	B-Lactam antibiotics (Penicillin, ampicillin, ceftriaxone)	Johns Hopkins/Columbia Univ., Palm Harbor, ALS Assoc.
	Benzodiazepine partial inverse agonist	737552	GlaxoSmithKline/Shionogi
	Others	MEM 1003	Memory Pharmaceuticals
		MEM 1414	Memory Pharmaceuticals
		MPC-7869	Myriad Genetics
		Rosiglitazone	GlaxoSmithKline
		Ladostigil hemitartrate	TEVA
		NS-2330	Boehringer Ingelheim
		SGS111	Saegis Pharmaceuticals
		SGS518	Saegis Pharmaceuticals
		SGS742	Saegis Pharmaceuticals
		SRA-333	Wyeth Pharmaceuticals

Source: R. Cacabelos, CIBE Database, 2006; Prous Science Database, 2006; Cacabelos et al (10); Cacabelos (12,13); Roses & Pangalos (50); Medicines in Development for Mental Illnesses 2003-2005 Survey.

NPI-D, GDS and ADCS-ADL ($p<0.05$); however, no major differences are observed between donepezil and rivastigmine in older patients. Younger patients with two wild-type BuChE alleles also have a significantly better response to rivastigmine than donepezil on the ADCS-ADL, probably due to the pharmacological properties of rivastigmine as an inhibitor of both AChE and BuChE, in contrast to donepezil which is an AChE-selective inhibitor (213). In a previous study, Wilkinson et al (210) had found that both donepezil and rivastigmine showed comparable improvements on the ADAS-Cog; however, more patients in the donepezil group (89.3%) completed the study compared with the rivastigmine group (69.1%); and 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued due to adverse events.

Studies evaluating predictors of nursing home placement (NHP) revealed that AD patients treated with donepezil (N=3864) or rivastigmine (N=1181) for more than 1 year had a similar reduced risk of NHP in a large insured American population as compared to controls (N=517). In the rivastigmine, donepezil, and control groups, 3.7%, 4.4% and 11.0% of subjects, respectively, had an NHP ($p<0.001$ for rivastigmine vs control) (214).

In a retrospective study comparing the effects of donepezil and rivastigmine in AD patients with symptoms suggestive of concomitant Lewy body pathology, changes from baseline after 2 years of treatment with rivastigmine were significantly better than those seen with donepezil on the SIB, MMSE and ADCS-ADL (215).

Significant differences between donepezil (10 mg/day) and vitamin E (2000 IU/day) have been found after evaluation of changes in the latency of P300 (P3)-related evoked potentials in mAD and sAD patients. Vitamin E induced increments in P3 latency in mAD and sAD after 6 months of treatment, with worsening of cognitive function; and donepezil induced significant P3 latency reduction in mAD and sAD cases, reaching a maximum at 3 months, with parallel improvement in ADAS-Cog and WAIS scales (216).

Shorter P300 latencies were associated with higher Wechsler Adult Intelligence Scale scores and with lower ADAS-Cog scores in AD (217).

Donepezil, at conventional doses, exhibited similar effects to other AChEIs (rivastigmine, galantamine) and superior effects to memantine on cognitive performance in APP23 mice (218). The neuroprotective effect of donepezil against Aß(1-42) toxicity in cholinergic neurons is not mediated by interference with the NMDA-mediated excitotoxic process, and donepezil is more effective than memantine against cholinergic neuronal damage induced by Aß(1-42) exposure (219).

Some basic studies have been designed to compare the effects of donepezil and galantamine due to their differential pharmacological profiles. The effects of donepezil and galantamine have been compared on nerve growth factor (NGF), high (TrkA and phosphor-TrkA)- and low (p75 neurotrophin receptor)-affinity NGF receptors, cholinergic markers (cholineacetyltransferase, vesicular acetylcholine transporter), and memory performance in aged rats. Both donepezil and galantamine enhanced spatial learning, but neither AChEI was associated with marked changes in NGF, NGF receptors, or vesicular acetylcholine transporter, although donepezil did moderately increase choline acetyltransferase in the basal forebrain and hippocampus. These results led to the conclusion that repeated exposures to either donepezil or galantamine results in positive and sustained behavioural and cholinergic effects in the aged mammalian brain but that the allosteric potentiating ligand activity of galantamine at nicotinic acetylcholine receptors may not afford any advantage over AChE inhibition alone (220). In an open-label study, Jones et al (221) found that donepezil was superior to galantamine in mAD; in contrast, significant advantages were found by Wilcock et al (222) in the treatment response to galantamine (versus donepezil) on cognition as measured by response rates on the MMSE and ADAS-Cog. The effects of donepezil have also been compared with those of galantamine on sleep in AD. Neither galantamine nor donepezil negatively affected sleep; however, on every measure, there were suggestions of slight more benefit associated with galantamine treatment, although confirmation of clinical significance is needed (223).

In a recent paper, Shearman et al (224) reported region- and drug-specific effects induced by donepezil and memantine on different neurotransmitters in the ventral and dorsal hippocampus and the prefrontal and medial temporal cortex assessed by mycrodialysis. Memantine resulted in significant increases in extracellular dopamine, norepinephrine, and their metabolites, in the cortical regions, and in a reduction of dopamine in the cortex and in the dorsal hippocampus.

Norepinephrine increased in the cortex after memantine administration, and increased in the hippocampus and in the medial temporal cortex in response to donepezil, decreasing in the ventral hippocampus. Both compounds decreased extracellular serotonin levels, and the metabolites increased in most areas. Curiously, memantine increased extracellular acetylcholine in the nucleus accumbens and the ventral tegmental area (224). Summarizing, in clinical terms, according to Birks (127), 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 (127).

Effects on Behavioral Symptoms and Functional Deficits

Dementia is clinically characterized by memory disorders, behavioural changes, and progressive functional decline. The estimated prevalence of psychiatric symptoms in AD accounts for 40-60% of the cases (225,226). 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 behaviour 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 (e.g., adrenoceptor antagonists, calcium channel blockers, diuretics, laxatives, antiemetic/antimotility, histamine antagonists, analgesics/antipyretics, antihyperglycaemics, etc) (227). In other cases, behavioural 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, antypsychotics may increase the risk of cerebrovascular accidents and also contribute to cortical atrophy after years of chronic treatment. The prevalence for specific features of psychotic symptoms is 28.8-46% for delusions, 16.9-34.3% for hallucinations (4.4-21.9% visual, 1.1-15.6% auditory) and 10-35% for misidentification syndromes. The annual incidence rate of psychotic symptoms is about 1-5.3%, with a duration of symptoms of about 2.4-4.2 years. Behavioral changes appear in 65% of institutionalized patients presenting the following features: escape, aggression, restlessness, wandering, regression and verbally disruptive behaviour. Positive psychotic symptoms are directly associated with behavioural disturbances. Mood-related symptoms, including depression, anxiety, slowed thinking, irritability, apathy, social withdrawal and suicidal talk are also very frequent in AD (15-75%). The major depressive syndrome occurs in approximately 15-30% of patients with dementia and in older medical patients. Although 40-60% respond to antidepressant and/or anxiolytic medication, both depression and anxiety-like symptoms contribute to a deterioration in living conditions of the patients and their relatives. In addition, motor dysfunction (70-100%), myoclonus (8-15%), convulsions (3-5%), incontinence (10-46%), other neurological symptoms (6-27%), cerebrovascular symptoms (50-73%), and other medical conditions (50-64%) also contribute to make the pharmacological management of patients with this type of dementia more complex (225,226). In this regard, it would be desirable that antidementia drugs do not increase the ADR rate currently seen in these patients, and that symptomatic medications for dementia ameliorate the behavioural disturbances that represent a strong predictor of institutionalization (225,226). Furthermore, behavioural symptoms in AD significantly increase the direct costs of care (US$10,670-16,141 higher annual costs in high-NPI as compared with low-NPI) (228). 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 (229,230). 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 (231). 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 (e.g., donepezil + risperidone) (207).

Several papers have documented the parallel beneficial effects of donepezil on cognition and behavioural symptoms in AD (198,232-236) (Table 2); however, some behavioural symptoms might also be exacer-

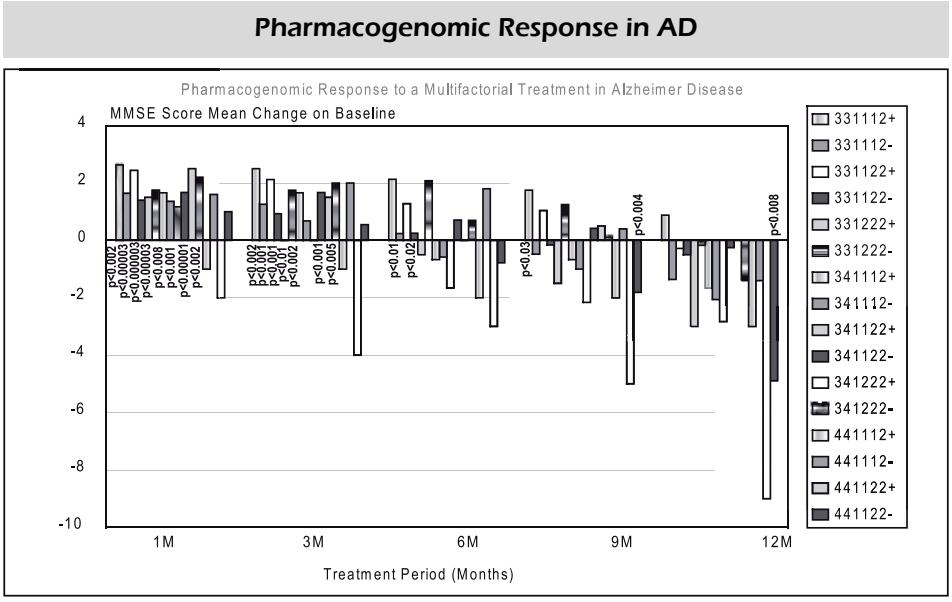


Figure 2. **Pharmacogenomic response to a multifactorial (combination) therapy in Alzheimer's disease. AD-related genotypes denote haplotype-like clusters integrating allelic variants associated with APOE, PS1, and PS2 genes. Adapted from Cacabelos (Ref. 33) and Cacabelos et al (188).**

bated by AChEIs. In clinical trials, sleep problems have been identified as side-effects of donepezil (Table 3). Poor sleep quality can exacerbate behavioural 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%) (237). In any case, behavioural symptoms are a major problem in the AD syndromic constellation (238) and, assuming that most psychotropic drugs contribute to deteriorate cognition and psychomotor function, as well as cerebrovascular function (239,240), AChEIs represent an option to be explored in more detail as a monotherapy or in combination with other psychotropic drugs at low doses (241,242).

DONEPEZIL IN CEREBROVASCULAR DISORDERS

Cerebrovascular dysfunction is a common finding in dementia (33,36,37,40,243-246); and mixed dementia (MXD) (degenerative + vascular) is the most frequent form of dementia in older patients (>75-80 yrs) (244-246). Diverse vascular risk factors (cardiovascular disorders, hypertension, hypotension, hypercholesterolemia, dyslipemia, atherosclerosis, diabetes) accumulate in patients with dementia and are at the basis of the pathogenic mechanisms leading to vascular dementia (VD) (244-246).

A growing number of studies emphasize on the importance of oxidative stress on aging and neurodegeneration (44). Mutations in mitochondrial DNA (mtDNA) accumulate in tissues of mammalian species promoting cell apoptosis and aging (247), and the inhibition of free radical formation in mitochondria reduces mtDNA deletions and enhances longevity (248). Recent evidence indicates that aging-related increase in oxidative stress correlated with developmental pattern of ß-secretase activity and ß-amyloid plaque formation in transgenic Tg2576 mice with AD-like pathology (249). Oxidative stress can be induced and/or exacerbated by ischemic events and chronic brain hypoperfusion leading to premature neuronal death in dementia (36,244-246). Donepezil is expected to have a protective effect against progressive degeneration of brain neuronal cells in ischemic cerebrovascular disease and AD (250).

Some neuropsychiatric symptoms (e.g., hallucinations) in dementia with Lewy bodies (DLB) and Parkinson's disease dementia may exacerbate due to regional hypoperfusion. A significant correlation between an increase in perfusion in midline posterior cingulated and decrease in hallucination severity, as well as a significant correlation between increased fluctuations of consciousness and increased thalamic and decreased inferior occipital perfusion have been observed in patients with DLB or Parkinson-dementia (251). Furthermore, transcriptional profiling of human brain endothelial cells defines a subset of age-dependent gene expression which is altered in AD and also probably in VD. The expression of the homeobox gene MEOX2 (GAX), a regulator of vascular differentiation, is low in AD. Restoring the expression of GAX in endothelial cells of the blood-brain barrier from AD patients stimulates angiogenesis, transcriptionally suppresses AFX1 forkhead transcription factor-mediated apoptosis and increases the levels of the low-density lipoprotein receptor-related protein 1 (LRP1), a major ß-amyloid peptide clearance receptor (252). It has also been postulated that a loss of cholinergic cerebrovascular control may contribute to the pathogenesis of AD, and that an increased brain perfusion rate might be part of the therapeutic effects of AChEIs in dementia, either AD or VD. The transcription of endothelial nitric oxide synthase depends on an adequate cholinergic innervation of microvessels, and vasoregulative abnormalities present in AD can be partially reversed by donepezil (253). Studies with donepezil (254,255), rivastigmine (256), and galantamine (257) have shown modest effects in VD. Improvements have been observed in cognition, behaviour and activities of the daily living in VD patients treated with donepezil in a similar fashion to those detected in AD (254,255,257-262). 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,

Table 5. Pharmacological effects of donepezil in humans and animals

Neurochemical Effects

Acetylcholinesterase inhibition
Up-regulation of nicotinic receptors in cortical neurons
Enhancement of brain cholinergic neurotransmission
Regulation of other neurotransmission systems (dopamine, noradrenaline)
Promotion of non-amyloidogenic pathways for APP processing
Potential capacity to reduce β-amyloid formation
Inhibition of β-amyloid aggregation
Enhancement of neurotrophic activity
Regulation of proinflammatory cytokines.
Sigma-1-receptor agonist activity
Protection against glutamate-related excitotoxicity
Inhibition of the increase of intracellular calcium concentration
Enhancement of the GH/IGF-1 axis in basal conditions and after GHRH stimulation
Improved vascular perfusion
Cerebrovascular protection
Antioxidant effect

Clinical Effects

Potential benefits in dementia and other CNS disorders
- Main effects in dementia (degenerative, vascular)
  - Improvement in cognition, behaviour and function
  - Slowing of disease progression
  - Slowing of annual hippocampal atrophy rate
- Improved cerebrovascular function in AD, VD, and DLB
- Reduced mortality rate in nursing home residents
- Reduced caregiver burden
- Improvement in the dysexecutive syndrome in Parkinson's disease
- Amelioration of compulsive hypersexual behaviour in Parkinson's disease
- Improvement in episodic memory in chronic amnesia syndrome due to brain haemorrhage
- Improvement in cognition, behaviour and function in traumatic brain injury
- Regulation of REM sleep (potential induction of dream abnormalities and nightmares?)
- Increase in brain perfusion
- Psychomotor improvement in pure akinesia
- Analgesic effect
- Psychostimulant effect in opiate-related sedation

Canada and Australia, revealed that donepezil groups showed significant improvements in cognition, global function, and ADLs (260). 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 (263,264). 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%) (265). 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.

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 (36,244-246). Glucose metabolism tends to decline over time in the bilateral precuneus and posterior cingulated gyri and in the frontal, temporal and parietal cortices of AD patients (266). 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 cingulated gyri, right middle temporal gyrus, right inferior parietal lobe, and prefrontal cortex after 1-year treatment with donenezil (267). 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 (268,269). In a small study (N=10), patients with vascular dementia improved their cognitive function and the latency of the P300 auditory event-related potentials after one month of treatment with donepezil (270). 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 (271). 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 (272). 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 (273). Donepezil has been used to potentiate learning in subjects with stroke by amplifying cholinergic input to the cerebral cortex from the nucleus basalis of Meynert (274). Nadeau et al (274) obtained positive results in the Wold Motor Function Test (WMFT) in patients with stroke using donepezil as an adjuvant to constraint-induced therapy for upper-limb dysfunction; however, other outcome measures, such as the Motor Activity Log, the Box and Block Test, the Actual Amount of Use Test, the Fugl-Meyer Motor-Scale-Upper Extremity, and the Caregiver Strain Index did not reveal any benefit with donepezil.

Impairments of memory are often seen after rupture and repair of aneurysms leading to a basal forebrain lesion. In chronic amnesia syndrome (>75 months) from a rupture and repaired aneurysm of the anterior communicating artery, the anterior cerebral or the pericallosal artery, Benke et al (275) found that donepezil significantly improved short and long delay free recall scores, whereas attentional and executive functions improve only non-significantly; these effects disappeared after drug discontinuation (275).

Aphasia is one the most common neurological symptoms after stroke (prevalence in Western Europe: 800 per 100,000), resulting in significant disability and handicap. Broca, Wernicke and global aphasia are severe forms of post-stroke language impairment with poor prognosis. Donepezil might also provide some benefit in patients with chronic post-stroke aphasia (276,277). In rats with cerebral infarction induced by permanent left middle cerebral artery occlusion, donepezil significantly attenuates cerebral infarction volume. This neuroprotective effect can be prevented by coinjection of mecamylamine, a nicotinic acetylcholine-receptor antagonist, indicating that cerebrovascular protection is mediated via nicotinic activation (278).

Diabetes mellitus is s risk factor for stroke and cerebrovascular dysfunction. Approximately 30-50% of the patients with diabetes develop cognitive deterioration and progressive cerebrovascular hypoperfusion. Parieto-temporal hypoperfusion, asymmetrical hypoperfusion and fronto-temporal hypoperfusion occur in more than 30% of diabetic patients accompanied by cognitive decline. In Japanese patients with diabetes, donepezil did not affect either cognition or brain perfusion after 3 months of treatment (279).

A growing danger in our society is the negative impact of coronary artery bypass grafting (CABG) on cognitive function. Cognitive deficits may manifest as psychological alterations (depressive symptoms, anxiety), short-term memory loss, executive dysfunction and psychomotor slowing. During the next 2-6 years after CABG intervention in people older than 60 years, approximately 10-20% of subjects may develop a cognitive decline compatible with incipient dementia. Proposed mechanisms of CABG-related brain dysfunction include surgical-related trauma, genetic susceptibility, microembolization, other vascular or ischemic changes, and temperature during surgery. AChEIs, memantine, and several nootropic drugs have been proposed as candi-

CYP2D6-Related Metabolizer Types

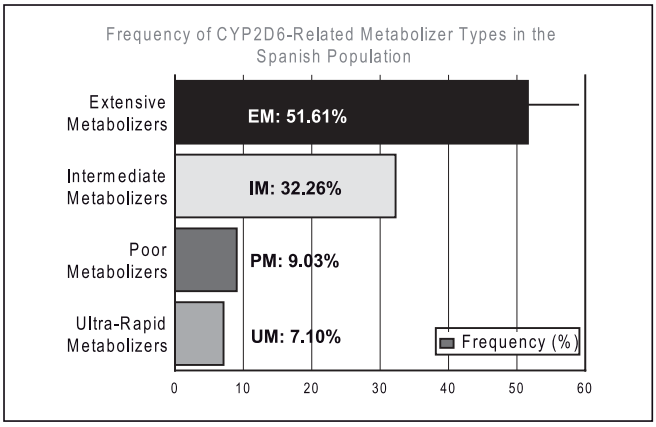


Figure 3. **CYP2D6-Related metabolizers types in the Spanish population. Adapted from Cacabelos (Ref. 497 & 498)**

date drugs to palliate memory decline in this population at risk (280).

Abnormal cutaneous vasodilatory responses to the iontophoresis of vasodilators (methacholine chloride, acetylcholine chloride, sodium nitroprusside) were observed in AD. Response to methacholine was enhanced by 78% in AD patients under therapy with donepezil, which was also able to increase perfusion after application of acetylcholine (68%) and sodium nitroprusside (46%) (281). There is now evidence to support a vasoconstrictive effect of Aß protein that can be detected in peripheral skin microvasculature. AChEIs are able to improve endothelial-mediated vascular responses to acetylcholine and bradykinin subsequent to perfusion of Aß peptides. Donepezil reduces the vasoconstrictor effect of Aß peptides and restores the endothelial vascular response to bradykinin (282).

DONEPEZIL IN OTHER CNS DISORDERS

Cholinergic dysfunction is not only seen in AD, but also in other forms of dementia (Lewy body dementia, vascular dementia, Parkinson dementia, fronto-temporal dementia, progressive supranuclear palsy, Huntington's disease) and also in other CNS disorders (Down syndrome, Korsakoff syndrome, post-traumatic brain damage, delirium, psychoses, etc). To palliate some of the symptoms present in these polymorphic pathologies, AChEIs have been proposed as an adjuvant therapy with controversial results.

Dementia with Lewy bodies and Parkinson dementia

In a report of the Quality Standards Subcommittee of the American Academy of Neurology, donepezil is recommended for dementia in Parkinson's disease, and rivastigmine for dementia with Lewy bodies (DLB); the board states that AChEIs are effective treatments for dementia in Parkinson's disease, but improvement is modest and motor side effects may occur (283).

Dementia with Lewy bodies (DLB) is a form of dementia with effects on cognition, mood, behaviour, and functioning, in which a cholinergic disturbance has been demonstrated. Preliminary data suggested that AChEIs may be efficacious in DLB, with improvement in cognition and hallucinations and worsening of parkinsonism (284-286), but methodological limitations (e.g., small sample sizes, paucity of standardized psychometric measures) do not permit to establish a clear conclusion at the present time (287). In a preliminary study in patients with DLB, Mori et al (288) found a significant improvement in NPI-11 scores after 12 weeks of treatment with donepezil (5 mg/day); however, cognition improved during the first 4 weeks of treatment, and stabilized or declined thereafter. This Japanese group concludes that donepezil is expected to be therapeutically useful and safe in treating DLB patients, who may benefit in terms of improvement in behavioural and psychological aspects of dementia rather than in cognitive deficit, without apparent effect on parkinsonism deterioration (288); however, catatonia and worsening of the parkinsonian symptoms have been reported in a 75-year-old Japanese woman with DLB (289). DLB patients receiving donepezil appear to show a significant reduction in slow wave activity in their EEGs, but this effect was not observed in patients with AD (290). Donepezil can also attenuate delusions and hallucinations in DLB in parallel with an increase in occipital rCBF, suggesting that functional visual association cortex deficits may cause visual hallucinations in patients with DLB (291).

In Parkinson's disease (PD), donepezil showed a modest benefit on aspects of cognitive function, with no apparent effect on psychomotor function and/or psychiatric symptoms (292-295). In a small number of PD patients, it has been reported that donepezil may improve hallucinations and delusions, although psychomotor deterioration appears in 25% of the cases (296). In a pilot study with 10 PD patients, donepezil induced an improvement on the CGI (Clinical Global Impression) and on both the modified Wisconsin Card Sorting Test and DIGIT Span, suggesting that donepezil may be useful in the treatment of the dysexecutive syndrome associated with PD (297). Similar results have been observed in both PDD and DLB after donepezil treatment, with improvements in cognition and behaviour, and no changes in psychomotor function (298). To specifically evaluate the impact of donepezil on motor function in PD, Mentis et al (299) performed a double-blind, placebo-controlled trial of 8 weeks with donepezil (10 mg/day) in 17 PD patients, and they found that neither donepezil nor the placebo altered motor kinematic measures. Nonetheless, donepezil has been proposed as a treatment for levodopa-induced dyskinesias. Some other effects of donepezil have been reported in single cases of PD, such as attenuation of compulsive hypersexual behaviour (300). A dramatic improvement in psychomotor function has been observed in a case of pure akinesia secondary to an episode of bacterial pneumococcal meningoencephalitis after treatment with donepezil, in parallel with a marked increase in the perfusion of the frontoparietal cortex (301).

When donepezil is co-administered with levodopa/carbidopa in PD, no clinically significant drug-drug interactions are observed at a steady state. The small changes in the pharmacokinetics of levodopa (changes

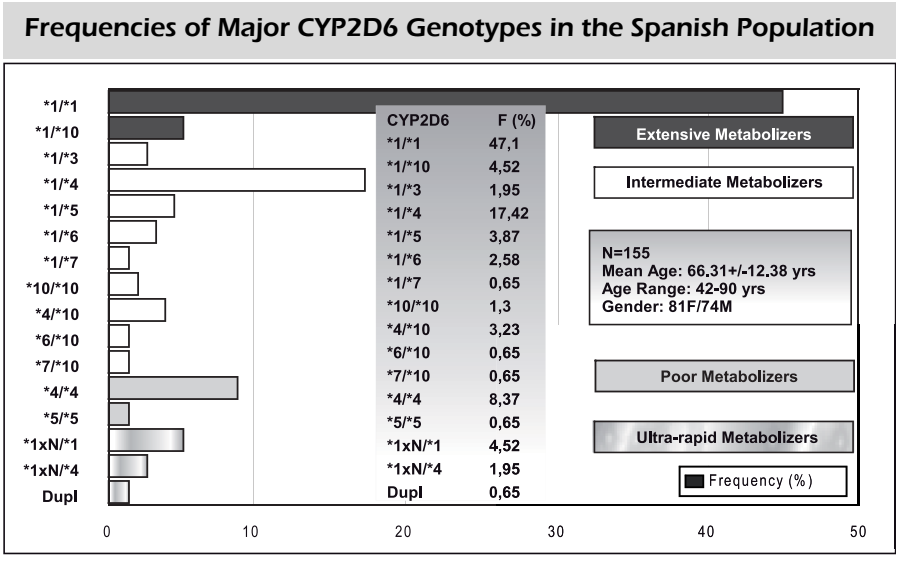


Figure 4. **Frequencies of major CYP2D6 genotypes in the Spanish population. Adapted from Cacabelos (Ref. 497 & 498)**

Table 6. Selected studies with donepezil in different types of CNS disorders

Author	Year	Disease	N	Study	Effect	Outcome Measures	Comments
Burt et al (365)	1999	Bipolar disorder	11	Open-label	Positive	Psychiatric assessment	Improvement in 50% of the cases
Greene et al (369)	2000	Multiple sclerosis	17	Open-label	Positive (12 w)	Cognition, neurologic, and behavioural assessment	Improvement in cognition, function and behaviour
Whelan et al (315)	2000	Traumatic brain injury	53	Open-label	Positive (2 y)	Wechsler Adult Intelligence Scale-Revised; Hooper Visual Organization Test	Improvement in cognition and psychiatric disturbances; Concomitant medication
Masanic et al (314)	2001	Traumatic brain injury	4	Open-label	Positive (8 w)	Rey Auditory Verbal Learning Test (RAVLT); Complex Figure Test (CFT); Rivermead Behavioural Memory Mest (RNMT); Neuropsychiatric Inventory (NPI)	Improvement in memory and behaviour
Caroff et al (353)	2001	Schizophrenia Schizoaffective disorder Tardive dyskinesia	10	Open-label	Positive (8 w)	Abnormal Involuntary Movement Scale; Brief Psychiatric Rating Scale; Mini-Mental State Examination; Barnes Akathisia Scale; Simpson-Angus Scale	90% positive response in TD
Kishnani et al (307)	2001	Down's syndrome	4	Open-label	Neutral (40.5 w)		No major side -effects
Prasher et al (308)	2002	Down's syndrome	30	Double-blind Placebo-controlled	Positive (24 w)	Dementia Scale for Mentally Retarded Persons (DMR) Severe Impairment Battery (SIB) Neuropsychiatric Inventory (NPI) Adaptive Behavior Scale (ABS)	Improvement in 50%
Lott et al (309)	2002	Down's syndrome	6	Open-label	Positive (5 m)	Down Syndrome Dementia Scale	Improvement in dementia scores
Hardan and Handen (358)	2002	Autism	8	Retrospective		Aberrant Behavior Checklist CGIS	Improvement in behaviour in 50% of the cases; Concomitant psychoactive medication
Aarsland et al (293)	2002	Parkinson's disease	14	Double-blind Placebo-controlled	Positive (10 w)	MMSE; CIBIC+	Cognitive improvement; No worsening of parkinsonism
Bergman and Lerner (356)	2002	Parkinson's disease	6	Open-label Add-on (+ antiparkinsonian drugs)	Positive (6 w)	Scale for the Assessment of Positive Symptoms Simpson-Angus Scale	Improvement of psychotic symptoms; no functional deterioration
Friedman et al (338)	2002	Schizophrenia	36	Double-blind Placebo-controlled Add-on (+ risperidone)	Negative (12 w)	Cognitive function	No effect
Sahin et al (323)	2002	Wernicke-Korsakoff's disease	7	Single-blind Placebo-controlled	Negative (30 d)	Neuropsychology; verbal and visual memory; attention; executive function	No effect
Buchanan et al (342)	2003	Schizophrenia	15	Open-label Add-on (+ Olanzapine)	Positive (6 w)	Praxis; neuropsychology; positive and negative symptoms	Moderate improvements
Slatkin and Rhiner (373)	2003	Opiate-related sedation	40	Retrospective	54 d	Clinical Global Improvement Scale (CGIS) Epworth Sleepiness Scale (ESS)	Improvement in sedation and global function
Bruera et al (331)	2003	Opiod-induced sedation	27	Open-label	Positive (7 d)	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)	General improvement
Johnson et al (305)	2003	Down's syndrome	19	Open-label	Neutral (12 w)	Cognition, Function, Language, Caregiver rating	Only improvement in language
Morey et al (316)	2003	Traumatic brain injury	7	Open-label	Positive (6 m)	Brief Visual memory Test (BVMT-R) Hopkins Verbal Learning Test Wechsler Adult Intelligence Scale-III Controlled Oral Word Association Test Memory Functional Questionnaire	Improvement on immediate and delayed memory
Nahas et al (345)	2003	Schizophrenia	6	Double-blind Placebo-controlled Add-on	Positive (12 w)	fMRI	Increase in frontal lobe and cingulated activity

Tugal et al (339)	2004	Schizophrenia	12	Double-blind Placebo-controlled Cross over	Negative (12 w)	Positive and Negative Syndrome Scale (PANSS) Calgary Depression Scale Wechsler Memory Scale Revised (WMS-R) Verbal Fluency Test Trail Making Test Wisconsin Card Sorting Test (WCST)	No effect in any area
Krupp et al (371)	2004	Multiple sclerosis	69	Double-blind Placebo-controlled	Positive (24 w)	Selective Reminding Test (SRT) Expanded Disability Status Scale	Improvement in memory performance
Erickson et al (341)	2005	Schizophrenia	15	Double-blind Crossover	Positive (18w)	Neurocognitive testing Psychiatric ratings	Inpatients Modest improvement in psychiatric symptoms and improved verbal learning
Mazza et al (348)	2005	Schizophrenia	14	Open-label	Positive (3-6 m)	Attention; Executive Function	Improvement in attention and executive function; Combination therapy: donepezil + risperidone
Ravina et al (295)	2005	Parkinson's disease	26	Double-blind Placebo-controlled Crossover	Neutral (10w)	ADAS-Cog; MMSE Unified Parkinson's Disease Rating Scale Mattis Dementia Rating Scale Brief Psychiatric Rating Scale	No worsening of parkinsonian symptoms
Freudenreich et al (340)	2005	Schizophrenia	36	Double-blind Placebo-controlled	Negative (8w)	Global cognitive assessment Psychopathological evaluation	Concomitant antipsychotic treatment
Beglinger et al (183)	2005	Healthy Elderly Subjects	26	Placebo-controlled	Negative (2w)	Global neuropsychological assessment	Deterioration in speed, attention, and short-term memory
Winhusen et al (372)	2005	Cocaine dependence	67	Placebo-controlled	Negative (10w)	Urine benzoylecgonine; Cocaine Clinical Global Impression Scale-Observer	Comparative with tiagabine and sertraline
Bergman et al (352)	2005	Tardive dyskinesia	7	Open-label	Positive (6 m)	Simpson-Angus Scale (SAS) tremor subscale	Significant effect after 4 weeks of treatment
Benke et al (275)	2005	Chronic amnesia due to aneurysm rupture	11	Open-label	Positive (8w)	California Veral Learning Test; tests of attention and of executive functions	Improve in episodic memory
Risch et al (347)	2005	Schizophrenia Schizoaffective disorder	13	Double-blind Crossover	Neutral (12w)	Depression	Antidepressive effect in conjunction with stable atypical antipsychotic medication
Niwa et al (279)	2005	Diabetes	92	Open-label	Negative (3 m)	Cognition; cerebral blood flow (SPECT)	38% cognitive dysfunction. No response
Mentis et al (299)	2005	Parkinson's disease	17	Double-blind Placebo-controlled	Positive (8w)	Kinematic measures	Donepezil did not alter motor function in PD
Liptzin et al (334)	2005	Post-surgical delirium	80	Double-blind Placebo-controlled	Negative (4 w)	Delirium Symptom Interview Confusion Assessment Method	No effect
Wilens et al (360)	2005	Attention-Deficit/Hyperactivity Disorder	13	Open-label	Negative (12 w)	ADHD Rating Scale Executive Function Checklist	No effect as an adjunctive therapy to psychostimulants
Christodoulou et al (370)	2006	Multiple sclerosis	69	Double-blind Placebo-controlled	Positive (24 w)	Selective Reminder Test Brief Repeatable Battery	65.7% responders
Eden Evins et al (364)	2006	Mania Bipolar disorder	12	Open-Label	Negative (8w)	Young Mania Rating Scale (YMRS) Hamilton Rating Scale for Depression (HAM-D) Brief Psychiatric Rating Scale (BPRS)	No effective as an adjunctive treatment for refractory manic symptoms
Shaw et al (375)	2006	Irradiated brain tumor	24	Open-label	Positive (24w)	Cognition, Mood, QoL	Low-grade glioma
Mazeh et al (354)	2006	Chronic schizophrenia	20	Add-on Double-blind Placebo-controlled	Negative (12 w)	Positive and Negative Symptom Scale (PANSS); CGI; ADAS-Cog	Elderly subjects; No effect

in AUC, Cmax, tmax) do not result in any change in motor symptoms in the short-term. Co-administration of the two drugs can lead to a small increase in adverse events compared with administration of levodopa/carbidopa alone in PD patients. These adverse events, however, are consistent with donepezil's cholinomimetic effect, and their incidence is comparable to those observed following the administration of donepezil alone (302).

In patients with progressive supranuclear palsy (PSP), donepezil caused a modest improvement on the Double Memory Test, but their ADLs and motor function significantly worsened (303). In another study, donepezil did not exert any benefit on either cognition or ADL in PSP (304).

Down's syndrome

Several trials with AChEIs in a reduced number of patients with Down syndrome showed modest results (305-312). A mild improvement in

cognitive functions and language, and a decrease in confusion, with occasional agitation and muscle weakness have been observed after treatment with donepezil (305-312). In patients with Down's syndrome donepezil may cause urinary incontinence (306), but this effect was not found in other studies (307).

Traumatic brain injury

Donepezil has been used in patients with post-traumatic brain damage. In small trials of several weeks to 2 years treatment, some improvement was reported in cognition, attention, behaviour and verbal memory in patients with traumatic brain injury (313-318). In a Finnish cohort of 111 outpatients with chronic traumatic brain injury, Tenovuo (319) identified 61% responders with positive effects in vigilance and attention, and no significant differences between donepezil and other AChEIs (galantamine, rivastigmine). In Switzerland, Khateb et al (320) detected modest cognitive improvement in 80% of their patients with traumatic brain injury under treatment with donepezil for 3 months, and some cases also improved on tests assessing speed of processing, learning and divided attention. Trovato et al (321) also found memory improvements in three adolescents with severe traumatic brain injury; two of them improved in total recall, long-term storage and consistency of long-term retrieval. Walker et al (318) did not find global differences in cognitive improvement between TBI and controls; but sub-set analyses suggested that administration of donepezil early in the rehabilitation stay was significantly related to higher rates of cognitive improvement.

Korsakoff's syndrome

The therapeutic effect of donepezil in patients with Korsakoff's syndrome was inconsistent (322,323), with minor effects on memory function at high doses in isolated cases (324). In 3 cases of Wernicke-Korsakoff syndrome, progressive partial improvement occurred in cognitive measurements through the treatment period (6-8 months), some of which was sustained after discontinuing donepezil (325).

Delirium and neurotoxicity

Since some cases of post-narcotic delirium, somnolence, or coma, interpreted as central cholinergic syndromes, have been reversed with physostigmine in the past (326), treatment with donepezil and other AChEIs have been attempted to reverse delirium caused by different medical conditions (e.g., pharmacological intoxication) with promising results (327-331). Animal studies exploring the antagonism of irreversible AChEIs such as soman and sarin have shown that pre-treatment with physostigmine, a reversible centrally acting AChEI, alone or in conjuction with the centrally acting anticholinergic drug, scopolamine, antagonizes the letality and toxicity of these agents. In a recent study, pre-treatment with donepezil significantly antagonized the symptoms induced in rats by the irreversible long-acting AChEI, diisopropylfluorophosphate (DFP) (332). A severe intractable delirium caused by basal forebrain vascular lesion and/or post-surgical lesions after craniopharingioma extirpation in a 68-year-old Japanese man was drastically recovered after treatment with donepezil. This case reported by Kobayashi et al (333) has to be interpreted with caution, since the patient was previously treated with antipsychotics, antidepressants and hypnotics, having hemorrhagic infarcts in the region of the diagonal band of Broca and nucleus basalis of Meynert. Delirium is a frequent complication of major surgery in older persons. The frequency of post-surgical delirium is about 15-20% during the first post-operative day; and subsyndromal delirium can appear in 50-70% of the cases during 1-3 post-operative days. In an older population (N=80) without dementia undergoing elected total joint-replacement surgery, in a double-blind, placebo-controlled study with donepezil, Liptzin et al (334) did not find any benefit as compared to placebo.

The reported analgesic effect of donepezil has been tested on patients with migraine in whom an apparent reduction in the number of crisis and pain severity was observed (330). In the pharmacological management of opioid-induced sedation in patients with chronic pain, methylphenidate, donepezil, and modafinil might be considered on appropriate patients (335).

Wheeler (336) reported the first study of topiramate-related cognitive and language dysfunction in 6 migraine patients who improved with donepezil treatment and allowed uninterrupted topiramate use.

Schizophrenia, psychosis and tardive dyskinesia

It has been postulated that the cognitive deficits present in schizophrenia might be due to a central cholinergic deficit. A donepezil add-on strategy might be useful in some selected cases of psychoses or schizophrenia in which a comorbid pathological process compromising the cholinergic system contributes to aggravate the psychotic syndrome (e.g., post-traumatic frontal damage, psychotic dementia, etc) (337). Addition of a cognitive enhancing medication to current antipsychotic therapy might improve functionality of networks necessary in working memory and internal concept generation. So far, most studies of donepezil in stable schizophrenic patients under antipsychotic medication did not show any relevant changes in cognition or other psychopathological symptoms (338-340). In some small studies under different therapeutic conditions, donepezil treatment was associated with modest

CYP2D6-GOT Activity

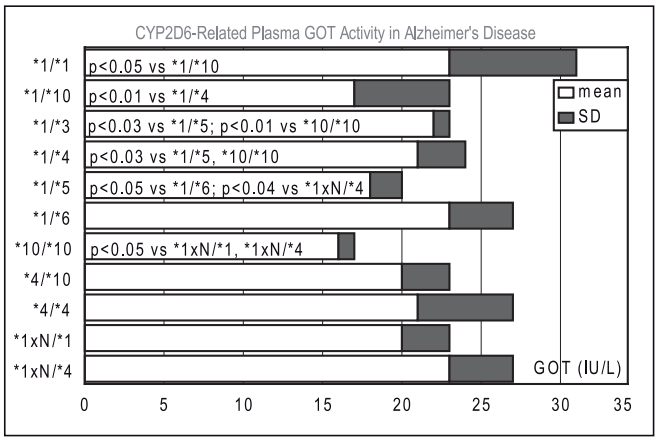


Figure 5. **CYP2D6-Related GOT activity in patients with Alzheimer's disease. Adapted from Cacabelos (Ref. 497 & 498)**

improvements in psychiatric symptoms and improved verbal learning (341). Donepezil + olanzapine treatment resulted in significant improvement in manual dexterity, and moderate improvements in verbal recall memory, visual memory and processing speed, with no changes in either positive or negative symptoms (342). Donepezil + olanzapine also showed some improvement in cognitive measures and increased activation of prefrontal cortex and basal ganglia on functional MRI in a schizoaffective disorder patient (343). The addition of donepezil to quetiapine improved memory in a 54-year-old female with schizophrenia (344). Donepezil addition to antipsychotic medication provided a functional normalization with an increase in left frontal lobe and cingulated activity when compared to placebo and from baseline fMRI scans (345). In a Japanese woman with Charles Bonnet syndrome, a clinical picture characterized by visual hallucinations in psychologically normal people, donepezil proved to be effective in reducing hallucinatory ideation (346). In schizophrenia and schizoaffective disorders under stable atypical antipsychotic medication, donepezil did not induce or worsen depressive symptoms, exhibiting a significant antidepressant effect (347). In a combined therapy with risperidone, donepezil improved attention, executive function, and understanding first order Theory of Mind in Italian patients with schizophrenia (348). Co-administration of donepezil and risperidone in schizophrenic patients for 7 days did not alter pharmacokinetic parameters of both compounds, and gastrointestinal side effects were similar in patients receiving donepezil + risperidone and those receiving donepezil alone (349). Repeated dosing with donepezil (5 mg/day x 2 weeks) had no significant effect on the safety, tolerability or pharmacokinetics of thioridazine in young volunteers, although thioridazine was poorly tolerated (350).

Taking into consideration basic studies, AChEIs may differ in their capacity to ameliorate learning and memory deficits produced by MK-801 in mice, which may have relevance for the cognitive effect of AChEIs in patients with schizophrenia. In this context, donepezil and physostigmine, but not galantamine, ameliorate MK-801-induced deficits in spatial reversal learning and in contextual and cued memory in a dose-dependent manner (351).

Donepezil has shown some benefit in cases of psychosis with tardive dyskinesia or in elderly patients with tardive movement disorders (352), but no positive effect could be demonstrated in schizophrenia (339), although preliminary studies reported an improvement of 90% in the patients with schizophrenia or schizoaffective disorders suffering tardive dyskinesia (353). In 20 elderly patients with chronic schizophrenia (mean duration of disease>20 years), Mazeh et al (354) did not find any effect of donepezil on negative signs and/or cognition. In a preliminary study, Stryjer et al (355) failed to demonstrate a clear effect of donepezil augmentation in clozapine treated chronic schizophrenic patients, although some patients showed improvement in the total PANSS scores. Tardive dyskinesia and other delayed-onset abnormal involuntary movement disorders may be induced by psychotropic drugs. In elderly patients with chronic tardive dyskinesia (>1 yr), treatment with donepezil was associated with a clinically significant improvement (37.5-63.6%) on the tremor subscale of the Simpson-Angus Scale (SAS) following 4 weeks of therpy (352). In some patients with PD, psychotic symptoms may improve with donepezil (356). An evaluation of earlier studies indicated that cholinergic drugs did not result in any substantial improvement in tardive dyskinesia symptoms when compared with placebo (357).

CYP2D6-GPT Activity

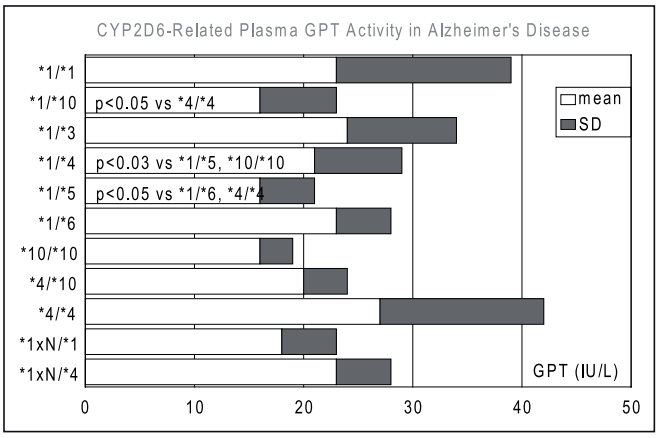


Figure 6. **CYP2D6-Related GPT activity in patients with Alzheimer's disease. Adapted from Cacabelos (Ref. 497 & 498)**

Autism, ADHD, and pervasive developmental disorders

The clinical experience with donepezil in autism is very limited. In a retrospective study of 8 cases, Hardan and Handen (358) found significant improvement in 50% of the children as assessed by the Aberrant Behavior Checklist and the Clinical Global Impression Scale. Decreases in the Irritability and Hyperactivity subscales were observed, but not changes in the Inappropriate Speech, Lethargy, and Stereotypies subscales were noted.

A number of youths with attention-deficit/hyperactivity disorder (ADHD) continue to experience residual symptoms and prominent executive function deficits resulting in impairments in multiple domains. In these cases, donepezil treatment has been proposed as an adjunct to stimulant medication to improve residual symptoms and executive function deficits; however, to date, no positive results have been observed with donepezil in ADHD (359,360). In 8 cases (10-17 years of age) with pervasive developmental disorder (PDD) and ADHD-like symptoms, Doyle et al (361) found improvement in ADHD-like symptomatology, especially in the areas of communication and socialization.

Donepezil has also been proposed as a candidate treatment for Tourette's syndrome (362). In a model for Tourette's syndrome (DOI-induced head twitch response (HTR) in mice), the anti-tic properties of donepezil, nicotine and haloperidol might be due to antagonism of cortical 5-HT2A receptors (362).

Depression and bipolar disorder

Donepezil treatment has also been tried in treatment-resistant bipolar mania with no apparent effect as an adjunctive therapy for refractory manic symptoms (364). In bipolar patients, when donepezil was added to current medication, 54.5% of the cases demonstrated marked improvement and 27.2% demonstrated slight improvement (365). The co-administration of once-daily oral donepezil (5 mg for 15 days) and

once-daily oral sertraline (50 mg for 5 days increased to 100 mg for 10 days) did not result in any clinically meaningful pharmacokinetic interactions, and no unexpected adverse events were observed in healthy volunteers (366). In non-geriatric patients with affective illness, donepezil can reduce memory loss, dry mouth, and constipation, but may trigger mania (367).

Multiple Sclerosis

Experimental allergic encephalomyelitis is the most widely used experimental model for multiple sclerosis (MS). A selective deficit in learning and memory performance is a consistent feature in rat encephalomyelitis, which correlates with a decline in choline acetyltransferase activity and nerve growth factor (NGF) mRNA level in the cerebral cortex, hippocampus, and basal forebrain. In this model, treatment with AChEIs (e.g., donepezil, rivastigmine) restores cognitive performance, choline acetyltransferase activity, and NGF mRNA expression (368). Initial studies with donepezil in MS revealed a modest improvement in cognition (attention, memory), executive function, and behaviour (369). In a recent study, donepezil improved memory performance in 65% of patients with multiple sclerosis (370). Similar results had been found by Krupp et al (371) in a trial with 69 MS patients who exhibited an improvement on the Selective Reminding Test (SRT) compared to placebo.

Other medical conditions

In patients with cocaine dependence, the effects of donepezil (10 mg/day) were compared with those of tiagabine (20 mg/day) or sertraline (100 mg). Subjective measures of cocaine dependence indicated significant improvement for all study groups; however, only the tiagabine group showed a significant decrease in urine benzoylecgonine level from baseline to weeks 5-8 (372). In patients with opiate-related sedation treated with opiate analgesic to palliate chronic pain, donepezil improved CGIS (Clinical Global Improvement Scale) and ESS (Epworth Sleepiness Scale) scores (373,374), as well as sedation, fatigue, anxiety, well-being, depression, anorexia and sleep disturbance; side effects included nausea, vomiting, diarrhoea, muscle and abdominal cramps, and anorexia (331).

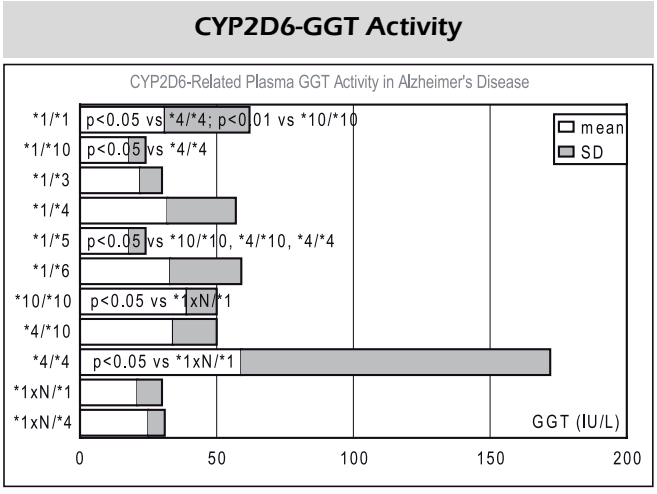


Figure 7. **CYP2D6-Related GGT activity in patients with Alzheimer's disease. Adapted from Cacabelos (Ref. 497 & 498)**

Donepezil has been used in patients with irradiated brain tumors (mainly low-grade gliomas) with promising results. In a 24-w open-trial with 24 patients, Shaw et al (375) observed improvement in attention/concentration, verbal memory, figural memory, verbal fluency, mood and quality of life. Since up to 90% of small cell lung cancer (SCLC) patients suffer cognitive dysfunction, donepezil and vitamin E treatment was tried in this pathology with poor results (376).

In patients with epilepsy, donepezil may increase cognition, but attention must be paid to possible exacerbation of seizures and drug-drug interactions with antiepileptics (377).

Isolated studies and single case reports also emphasize on the potential positive effects of donepezil in frontotemporal dementia, alcohol-related dementia (378), opiod-induced delirium (374), chronic drug users (379), schizophrenics with frontal lobotomy, and delirium due to amitriptyline intoxication (380).

SIDE-EFFECTS AND MAJOR ADVERSE DRUG REACTIONS (ADRs)

Side-effects and ADRs associated with donepezil (Table 3) can be classified into two main categories: common side-effects, most of them observed in clinical trials with AD patients, and infrequent extraordinary side-effects, seen in especial conditions or in small clusters of patients with different pathologies under treatment with other concomitant medications. The most frequent ADRs occurring in more than 5% of patients treated with donepezil include body events (45%), cardiovascular problems (18%), alterations in the digestive system (34%), haematic 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) (22,67,79,158,381-388) (Table 3). Other important side-effects observed in patients treated with donepezil include agitation, aggressive and violent behaviour 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) (389,390), a fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy in an 83-year-old woman (391), purpuric rash in an 82-year-old woman receiving long-term treatment with atenolol and doxazosin (392), hypnopompic hallucinations (393), urinary incontinence (394), extrapyramidal syndrome (395,396), seizures (397), pancreatitis, syncope (387), mania (367,398), violent behaviour (399) and other rare ADRs in isolated cases with different pathologies (Table 3).

Donepezil may adversely influence cardiovascular autonomic control (400). 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) (401). In patients receiving donepezil for more than one 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 (402).

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 triclycics (imipramine, maprotiline), or with antipsychotics (risperidone, olanzapine, quetiapine, thioridazine), antihistaminics, and antiepileptics. Donepezil can aggravate extrapyramidal symptoms when co-administered with atypical antipsychotics (e.g., 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, warfarine, digoxin, ginkgo biloba, piracetam, CDP-choline, anapsos, topiramate) do not show clinical relevance (72,73-76,200,202,302,336,349,350,366), except in isolated cases (395,403). 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 (77). A case of malignant-like syndrome due to donepezil and maprotiline has been reported (404). Another case of malignant syndrome has been reported in a 68-year-old Japanese patient with a history of delusions and hallucinations under treatment with bromperidol (12 mg) and donepezil (5 mg) (405). Donepezil may also interact with some anaesthetics.

It can not be excluded that donepezil acts on muscle plaque, blocking actylcholine 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 (406). Suxamethonium and donepezil may also be a cause of prolonged paralysis (407).

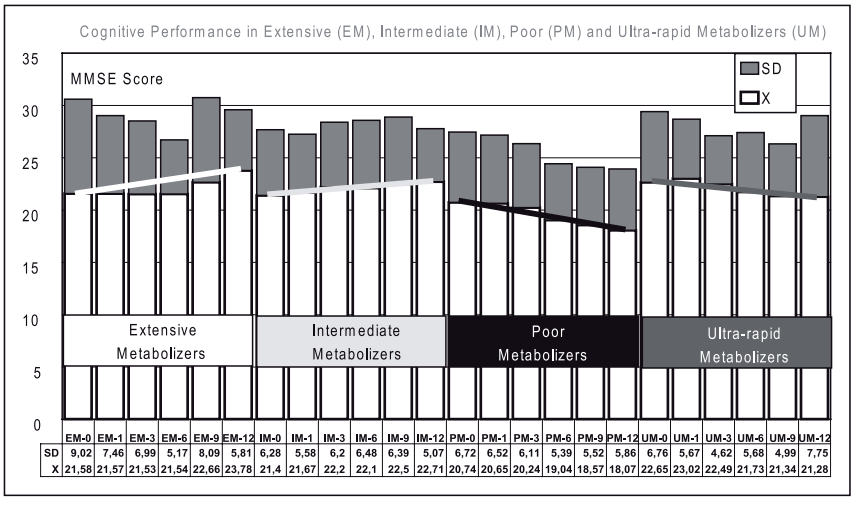
Recent findings indicate that donepezil users may experience changes in lipid profile. Statistically significant higher levels of triglycerides, cholesterol, LDL-cholesterol, and VLDL-cholesterol have been found in donepezil users as compared with non-users (408). Moreover, high cholesterol levels correlated with a faster decline at 1-year follow-up in AD patients on AChEI therapy (409). 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 (13,33,36,37,245,246). If donepezil-induced cholesterol alterations are confirmed in well-controlled trials, in which genotype-related patient stratification is highly recommended, then donepezil should be avoided in susceptible cases.

DISCONTINUATION AND SWITCHING POLICIES

The main reasons to discontinue the treatment with donepezil are intolerable ADRs, a narrow therapeutic window, lack of therapeutic effect, loss of efficacy in the long-term, cost-effectiveness conflict, personal taste of the physician, and marketing pressure. Since other AChEIs are available, the typical behaviour of clinicians is to switch from donepezil to other AChEI or to memantine. The sudden withdrawal of donepezil can be detrimental in some cases, producing acute cognitive and behavioural decline (410). Some studies indicate that patients showing no effect with donepezil or having important side-effects can benefit from treatment with other AChEIs (411). According to Giacobini (4), approximately 50% of patients with AD may benefit from treatment with a second AChEI (412-414). In the US population, 31.2% (583/1871) of donepezil patients discontinue treatment within 60 days of starting therapy (rivastigmine, 30.4%, 171/563). For the cohort of patients that remain on therapy (>60 days), the mean time to treatment discontinuation is 234-331 days for rivastigmine patients versus 235-337 days for donepezil patients (415,416). Patients are more likely to discontinue or switch their initial AChEI if they used a CNS medication before initiation of therapy. Patients who are newly diagnosed with AD and initiate therapy with either donepezil or rivastigmine have similar levels of persistency with their initial AD therapy in a real-world setting (416).

To determine the value of continued donepezil treatment in AD patients for whom clinical benefit was initially judged to be uncertain, Johannsen et al (388) performed a study consisting of 3 phases: (a) a 12-24-week, pre-randomization, open-label donepezil-treatment phase; (b) a 12-week, randomised, double-blind, placebo-controlled phase; and (c) a 12-week, sigle-blind donepezil treatment phase. In 619 patients who completed the open-label phase, the Danish group found 69% responders with clear clinical benefit and 31% non-responders; 202 patients were randomised to continue donepezil treatment (N=99) or placebo (N=103), and at the end of the trial, differences in favour

CYP2D6-Related Therapeutic Response in Alzheimer's Disease



	EM-0	EM-1	EM-3	EM-6	EM-9	EM-12	IM-0	IM-1	IM-3	IM-6	IM-9	IM-12	PM-0	PM-1	PM-3	PM-6	PM-9	PM-12	UM-0	UM-1	UM-3	UM-6	UM-9	UM-12
SD	9,02	7,46	6,99	5,17	8,09	5,81	6,28	5,58	6,2	6,48	6,39	5,07	6,72	6,52	6,11	5,39	5,52	5,86	6,76	5,67	4,62	5,68	4,99	7,75
X	21,58	21,57	21,53	21,54	22,66	23,78	21,4	21,67	22,2	22,1	22,5	22,71	20,74	20,65	20,24	19,04	18,57	18,07	22,65	23,02	22,49	21,73	21,34	21,28

Figure 8. **CCYP2D6-Related therapeutic response in Alzheimer's disease. Cognitive performance in extensive (EM), intermediate (IM), poor (PM) and ultra-rapid metabolizers (UM). Adapted from Cacabelos (Ref. 497 & 498)**

of continued donepezil vs placebo were observed in cognition (MMSE, 1.13, $p<0.02$) and behaviour (NPI, -3.16, $p<0.02$), with a non-significant trend favouring donepezil in activities of the daily living (ADL) and no significant changes in ADAS and DAD. In this study, most patients showed some clinical benefit during initial donepezil treatment; and among patients for whom clinical benefit was uncertain, improvement in cognition and behaviour were observed for those who continued donepezil treatment compared with the group switched to placebo. These observations led the Danish group to conclude that initial decline or stabilisation does not necessarily indicate a lack of efficacy in AD, and that the decision to discontinue treatment should be based on an evaluation of all domains (cognition, behaviour and ADL) and performed at several time intervals (388). Other authors suggest that when patients fail on donepezil or galantamine, switching to rivastigmine may improve cognition and behaviour; should they continue to deteriorate, the addition of memantine might be beneficial (417). In normal conditions, transitioning patients from donepezil to rivastigmine without a washout period is safe and well tolerated (418). Similar results have been obtained in other studies, suggesting that AD patients deteriorating on selective AChEI (donepezil) treatment can benefit from switching to a dual AChE-BuChEI (rivastigmine), in terms of stabilization of disease, improvement in cognitive function and reduction in the burden of concomitant psychoactive treatment (419). Cases of insomnia, dyskinesia, agitation, and delirium have been observed in patients with dementia with Lewy bodies switched from donepezil to galantamine (420).

It has been postulated that discontinuation of cholinesterase inhibition may decrease the effect of AChEIs in a second therapeutic intervention with the same drug or with a new AChEI (4). Similarly, it is a current observation that patients who, having been treated with AChEIs and after a wash-out period enter in a new clinical trial, respond more poorly to the novel compound than naïve patients previously untreated (Cacabelos et al., unpublished data); however, in a Post-Marketing Surveillance (PMS) study, Klinger et al (421) in Germany found that donepezil was shown to be efficacious and well tolerated in patients who were being insufficiently treated with memantine or nootropic therapy. In this study, the magnitude of response was similar to that observed in patients who were previously treatment naïve, suggesting that previous medication may not affect donepezil's efficacy (421). Post-hoc analyses of clinical trials that enrolled patients with and without previous exposure to AChEIs indicated that the efficacy and tolerability of a second and different AChEI were similar in both populations of patients. These findings may suggest that discontinuation of prior AChEI treatment is not predictive of future poor response to an effective treatment (422).

PHARMACOGENETICS AND PHARMACOGENOMICS

With the advent of recent knowledge on the human genome (423) and the identification and characterization of AD-related genes (13,32,33), as well as novel data regarding CYP family genes and other genes whose enzymatic products are responsible for drug metabolism in the liver (e.g., 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 (12,13,33,192-194) and in many other complex disorders (424,425), assuming that genetic factors are determinant for both premature neuronal death in AD (34-36) and drug metabolism (426). With pharmacogenetics we can understand how genomic factors associated with genes encoding enzymes responsible for drug metabolism regulate pharmacokinetics and pharmacodynamics (mostly safety issues) (427-429). 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 (426-431). 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 (32). In addition, it is very unlikely that a single drug will be able to reverse the multifactorial mechanisms associated with premature neuronal death in most dementing processes with a complex phenotype represented by memory decline, behavioural 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 (i.e., hypertension, cardiovascular disorders, diabetes, hypercholesterolemia, etc).

Although drug effect is a complex phenotype that depends on many factors, it is estimated that genetics accounts for 20 to 95% of variability in drug disposition and pharmacodynamics (428). Cholinesterase inhibitors currently in use for AD, such as donepezil and galantamine (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) (12,13) (Tables 1 & 3).

AD patients are currently treated with cholinesterase inhibitors, neuroprotetive drugs, antidepressants, anxyolitics, anti-parkinsonian drugs, anticonvulsants and neuroleptics at a given time of the disease clinical course to palliate memory dysfunction, behavioral changes, sleep disorders, agitation, depression, parkinsonism, myoclonus and seizures or psychotic symptoms (10,432). 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 [74]. Polymorphic variants in these genes can induce alterations in drug metabolism altering the efficacy and

Table 7. First generation of pharmacogenomic studies in Alzheimer disease with cholinesterase inhibitors, non-cholinergic drugs and multifactorial therapy

Drug	Type	Genotype	Study type	Result	Comment
Tacrine	Cholinesterase inhibitor	APOE	Retrospective	Genotype-dependent	Controversial results depending upon authors and study model
Donepezil	Cholinesterase inhibitor	APOE	Retrospective	Genotype-dependent	Controversial results depending upon authors and study model
Rivastigmine	Cholinesterase inhibitor	APOE	Retrospective	Unclear	Unconclusive data
Galantamine	Cholinesterase inhibitor	APOE	Prospective Retrospective	Unrelated Genotype-dependent	Controversial results depending upon authors and study model
CDP-choline	Choline donor Endogenous nucleotide	APOE	Prospective	Genotype-dependent	Replicated in 2 studies
Anapsos	Immunotrophic agent Natural product	APOE	Prospective	Genotype-dependent	Replicated in 2 studies
Memantine	NMDA antagonist	APOE PS1 PS2	Prospective	Genotype-dependent (Apoptosis)	One study Gene-to-gene analysis
Cerebrolysin	Neurotrophic factor	APOE	Prospective	Unrelated	One study Monogenic
CDP-choline Piracetam Anapsos	Combination therapy Endogenous nucleotide + Nootropic agent + Neuroimmunotrophic	APOE PS1 PS2	Retrospective	Genotype-dependent Cluster-dependent	Genomic analysis integrating APOE+PS1+PS2 in a trigenic matrix model Replicated in 2 studies
CDP-choline Piracetam	Combination therapy	APOE PS1 PS2	Prospective	Genotype-dependent Cluster-dependent	One study Monogenic + trigenic cluster analysis
CDP-choline Piracetam	Combination therapy	PRNP-M129V	Retrospective	Unrelated	One study Monogenic analysis
CDP-choline Piracetam	Combination therapy	APOE PS1 PS2 PRNP	Retrospective	Cluster-dependent	One study Tetragenic cluster analysis
CDP-Choline Piracetam Nicergoline Donepezil	Combination therapy	APOE PS1 PS2 ACE AGT APP MAPT	Prospective	Cluster-dependent	One study Polygenic cluster analysis
CDP-Choline Piracetam Nicergoline Donepezil	Combination therapy	CYP2D6	Prospective	Genotype-dependent	One study

Source: R. Cacabelos, CIBE Database, 2006. Adapted from Cacabelos (12,23)

safety of the prescribed drugs (433).

Drug metabolism includes phase I reactions (i.e., oxidation, reduction, hydrolysis) and phase II conjugation reactions (i.e., acetylation, glucuronidation, sulfation, methylation) (429). The typical paradigm for the pharmacogenetics of phase I drug metabolism is represented by the cytochrome P-450 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 monooxigenase 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 (32,426-429).

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). 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 (glutathion S-transferase A), GST-P, GST-T, GST-M, NAT2 (N-acetyl transferase), NAT1, and others (434). The most important enzymes of the P450 cytochrome family in drug metabolism by decreasing order are CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP2A6 (433-438). The predominant allelic variants in the CYP2A6 gene are CYP2A6*2 (Leu160His) and CYP2A6del. The CYP2A6*2 mutation inactivates the enzyme and is present in 1-3% of Caucasians. The CYP2A6del mutation results in no enzyme activity and is present in 1% of Caucasians

and 15% of Asians (13,434). The most frequent mutations in the CYP2C9 gene are CYP2C9*2 (Arg144Cys), with reduced affinity for P450 in 8-13% of Caucasians, and CYP2C9*3 (Ile359Leu), with alterations in the specificity for the substrate in 6-9% of Caucasians and 2-3% of Asians (13,434). The most prevalent polymorphic variants in the CYP2C19 gene are CYP2C19*2, with an aberrant splicing site resulting in enzyme inactivation in 13% of Caucasians, 23-32% of Asians, 13% of Africans, and 14-15% of Ethiopians and Saoudians, and CYP2C19*3, a premature stop codon resulting in an inactive enzyme present in 6-10% of Asians, and almost absent in Caucasians (13,434,435). The most important mutations in the CYP2D6 gene are the following: CYP2D6*2xN, CYP2D6*4, CYP2D6*5, CYP2D6*10 and CYP2D6*17 (13,436,437). The CYP2D6*2xN mutation gives rise to a gene duplication or multiplication resulting in an increased enzyme activity which appears in 1-5% of the Caucasian population, 0-2% of Asians, 2% of Africans, and 10-16% of Ethiopians. The defective splicing caused by the CYP2D6*4 mutation inactivates the enzyme and is present in 12-21% of Caucasians. The deletion in CYP2D6*5 abolishes enzyme activity and shows a frequency of 2-7% in Caucasians, 1% in Asians, 2% in Africans, and 1-3% in Ethiopians. The polymorphism CYP2D6*10 causes Pro34Ser and Ser486Thr mutations with unstable enzyme activity in 1-2% of Caucasians, 6% of Asians, 4% of Africans, and 1-3% of Ethiopians. The CYP2D6*17 variant causes Thr107Ile and Arg296Cys substitutions which produce a reduced affinity for substrates in 51% of Asians, 6% of Africans, and 3-9% of Ethiopians, and is practically absent in Caucasians (13,434,436,437).

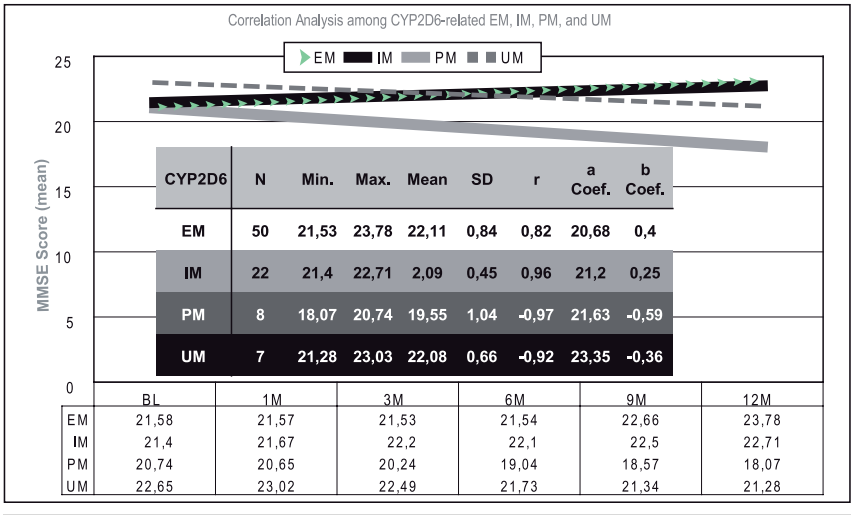
There are more than 200 P450 genes identified in different species. Saito et al (438) provided a catalogue of 680 variants among 8 CYP450 genes, 9 esterase genes, and 2 other genes in the Japanese population. The microsomal, membrane-associated, P450 isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2E1, 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.

Polymorphisms in genes associated with phase II metabolism enzymes, such as GSTM1, GSTT1, NAT2 and TPMT are well understood, and information is also emerging on other GST polymorphisms and on polymorphisms in the UDP-glucuronosyltransferases and sulfotransferases. Most of these polymorphisms exhibit geographic and ethnic differences (439-443). 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). Most drugs act as substrates, inhibitors or inducers of CYP enzymes. Enzyme induction enables some xenobiotics to accelerate their own biotransformation (auto-induction) or the biotransformation and elimination of other drugs (13). A number of P450 enzymes in human liver are inducible. Induction of the majority of P450 enzymes occurs by an increase in the rate of gene transcription and involves ligand-activated transcription factors, aryl hydrocarbon receptor, constitutive androstane receptor (CAR), and pregnane X receptor (PXR) (444,445). In general, binding of the appropriate ligand to the receptor initiates the induction process that cascades through a dimerization of the receptors, their translocation to the nucleus and binding to specific regions in the promoters of CYPs (445). CYPs are also expressed in the CNS, and a complete characterization of constitutive and induced CYPs in brain is essential for understanding the role of these enzymes in neurobiological functions and in age-related and xenobiotic-induced neurotoxicity (446).

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 (10). This may be due to different factors, including pharmacokinetic and pharmacodynamic properties of drugs, nutrition, liver function, concomitant medications, and individual genetic factors. 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 (e.g., efficacy, safety) (3,4,10). Therefore, the individualization of therapy or pharmacological tailorization in AD and other CNS disorders is just a step forward of the longstanding goal of molecular pharmacogenomics (447-449) taking advantage from the information and procedures provided by the sequencing of the entire human genome (422).

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) (450-452). For example, APOE-4 carriers show a less significant therapeutic response to tacrine (60%) than patients with no APOE-4 (450). In another study the frequency of APOE-4 alleles was higher in responders to a single oral dose of tacrine (452). It has been demonstrated that 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 respon-

CYP2D6-Related Cognitive Progression in Alzheimer's Disease



CYP2D6	N	Min.	Max.	Mean	SD	r	a Coef.	b Coef.
EM	50	21,53	23,78	22,11	0,84	0,82	20,68	0,4
IM	22	21,4	22,71	2,09	0,45	0,96	21,2	0,25
PM	8	18,07	20,74	19,55	1,04	-0,97	21,63	-0,59
UM	7	21,28	23,03	22,08	0,66	-0,92	23,35	-0,36

	BL	1M	3M	6M	9M	12M
EM	21,58	21,57	21,53	21,54	22,66	23,78
IM	21,4	21,67	22,2	22,1	22,5	22,71
PM	20,74	20,65	20,24	19,04	18,57	18,07
UM	22,65	23,02	22,49	21,73	21,34	21,28

Figure 9. **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 one-year treatment period with a multifactorial therapy. Adapted from Cacabelos (Ref. 497 & 498)**

se (450). Others found no differences after 6 moths 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 (453). It has also been shown that the APOE genotype may influence the biological effect of donepezil on APP metabolism in AD (454). Prospective studies with galantamine in large samples of patients in Europe (455) and in USA (456) 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 (457). MacGowan et al (458) 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 (459,460). In a recent study, Petersen et al (175) showed that APOE-4 carriers exhibited a better response to donepezil. Similar results have been found by Bizzarro et al (461); however, Rigaud et al (460) 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) (462,463) suggesting that APOE-associated factors may influence drug activity in the brain either by directly acting on neural mechanisms or by indirectly influencing diverse metabolic pathways (464).

To date, few studies have addressed in a prospective manner the impact of pharmacogenetic and pharmacogenomic factors on AD therapeutics (Table 7). Since APOE, PS1 and PS2 genes participate in AD pathogenesis regulating neuronal function and brain amyloidogenesis, in an attempt to envision the potential influence of major AD-associated genes on the therapeutic response in AD patients, we have performed the first pharmacogenomic study in AD using a genetic matrix model (trigenic haplotype-like model) to identify the response of a multifactorial therapy in different AD genotypes combining allelic associations of APOE+PS1+PS2 genes (192). With this strategy we have demonstrated that the therapeutic response in AD is genotype-specific, with APOE-4/4 carriers as the worst responders, and that some polymorphic variants exert a dominant effect on treatment outcomes (12,13,188,192-194) (Fig. 1 & 2). From these studies we can conclude the following: (i) Multifactorial treatments combining neuroprotectants, endogenous nucleotides, nootropic agents, vasoactive substances, cholinesterase inhibitors, and NMDA antagonists associated with metabolic supplementation on an individual basis adapted to the phenotype of the patient may be useful to improve cognition and slow-down disease progression in AD. (ii) In our personal experience the best results have been obtained combining (a) CDP-choline with piracetam and metabolic supplementation, (b) CDP-choline with piracetam and anapsos, (c) CDP-choline with piracetam and cholinesterase inhibitors (donepezil, rivastigmine), (d) CDP-choline with memantine, and (e) CDP-choline, piracetam and nicergoline. (iii) Some of these combination therapies have proven to be effective, improving cognition during the first 9 months of treatment, and not showing apparent side-effects. (iv) The therapeutic response in AD seems to be genotype-specific under different pharmacogenomic conditions. (v) In monogenic-related studies, patients with the APOE-2/3 and APOE-3/4 genotypes are the best responders, and APOE-4/4 carriers are the worst responders. (vi) PS1- and PS2-related genotypes do not appear to influence the therapeutic response in AD as independent genomic entities; however, APP, PS1, and PS2 mutations may drastically modify the therapeutic response to conventional drugs. (vii) In trigenic-related studies the best responders are those patients carrying the 331222-, 341122-, 341222-, and 441112- genomic clusters. (viii) A genetic defect in the exon 5 of the PS2 gene seems to exert a negative effect on cognition conferring PS2+ carriers in trigenic clusters the condition of poor responders to combination therapy. (ix) The worst responders in all genomic clusters are patients with the 441122+ genotype. (x) The APOE-4/4 genotype seems to accelerate neurodegeneration anticipating the onset of the disease by 5-10 years; and, in general, APOE-4/4 carriers show a faster disease progression and a poorer therapeutic response to all available treatments than any other polymorphic variant (12,13,188,192-194). (xi) Pharmacogenomic studies using trigenic, tetragenic or polygenic clusters as a harmonization procedure to reduce genomic heterogeneity are very useful to widen the therapeutic scope of limited pharmacological resources (12,13).

CYP2D6-Related Therapeutic Response

The CYP2D6 enzyme, encoded by a gene that maps on 22q13.1-13.2, catalyses the oxidative metabolism of more than 100 clinically important and commonly prescribed drugs such as cholinesterase inhibitors (tacrine, donepezil, galantamine), antidepressants, neuroleptics, opioids, some ß-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 (12,13,437,79). 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) (465). 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 (12,13,437). 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% (12,13,437).

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 alleles involved) (12,13,465-467, 497, 498).

In the Spanish population, where the mixture of ancestral cultures has occurred for centuries, the distribution of the CYP2D6 genotypes differentiates 4 major categories of CYP2D6-related metabolyzer types: (i) Extensive Metabolizers (EM) (*1/*1, *1/*10); (ii) Intermediate Metabolizers (IM) (*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10); (iii) Poor Metabolizers (PM) (*4/*4, *5/*5); and (iv) Ultra-rapid Metabolizers (UM) (*1xN/*1, *1xN/*4, Dupl). In this sample we have found 51.61% EMs, 32.26% IMs, 9.03% PMs, and 7.10% UMs (497, 498) (Fig. 3). The distribution of all major genotypes is the following: *1/*1, 47.10%; *1/*10, 4.52%; *1/*3, 1.95%; *1/*4, 17.42%; *1/*5, 3.87%; *1/*6, 2.58%; *1/*7, 0.65%; *10/*10, 1.30%; *4/*10, 3.23%; *6/*10, 0.65%; *7/*10, 0.65%; *4/*4, 8.37%; *5/*5, 0.65%; *1xN/*1, 4.52%; *1xN/*4, 1.95%; and Dupl, 0.65% (497,498) (Fig. 4). These results are similar to other previously reported by Sachse et al (436), Bernal et al (467), Cacabelos (12,13), Bernard et al (468) and others in the Caucasian population (437,440,441,444,469-471).

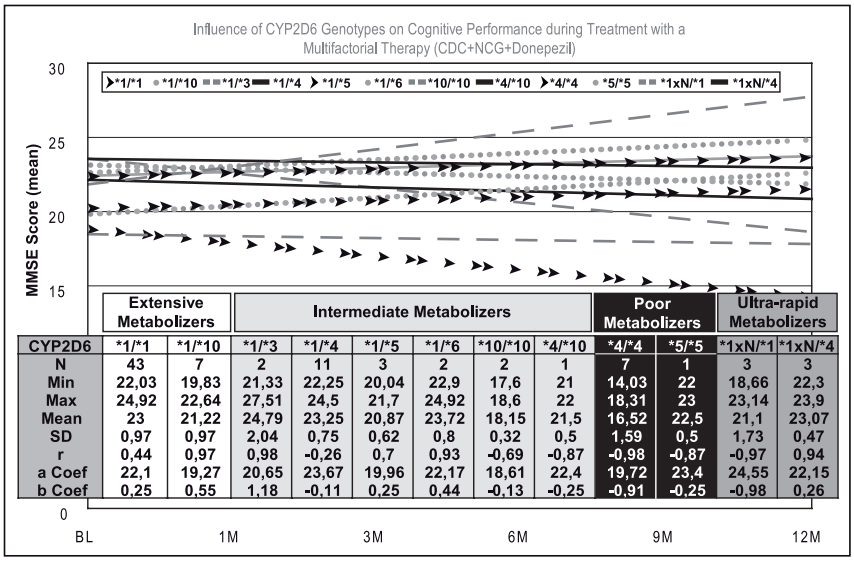
When comparing AD cases with controls, we observed that EMs are more prevalent in AD (*1/*1, 49.42%; *1/*10, 8.04%) (total AD-EMs: 57.47%) than in controls (*1/*1, 44.12%; *1/*10, 0%) (total C-EMs: 44.12%). In contrast, IMs are more frequent in controls (41.18%) than in AD (25.29%), especially the *1/*4 (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%) (472, 497, 498).

Although initial studies postulated the involvement of the CYP2D6B mutant allele in Lewy body formation in both Parkinson's disease and the Lewy body variant of AD, as well as in the synaptic pathology of pure AD without Lewy bodies (473), subsequent studies in different ethnic groups did not find association between AD and CYP2D6 variants (471,474-479). Notwithstanding, 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 (472, 497, 498).

Some conventional anti-dementia drugs (tacrine, donepezil, galantamine) are metabolized via CYP-related enzymes, especially CYP2D6, CYP3A4, and CYP1A2 (81,86), and polymorphic variants of the CYP2D6 gene can affect the liver metabolism, safety and efficacy of some cholinesterase inhibitors. In order to elucidate whether or not CYP2D6-related variants may influence transaminase activity, we have studied the association of GOT, GPT, and GGT levels with the most prevalent CYP2D6 genotypes in AD. In general terms, UMs and PMs tend to show the highest GOT activity and IMs the lowest. Significant differences appear among different IM-related genotypes. The *10/*10 genotype exhibited the lowest GOT activity with marked differences as compared to UMs ($p<0.05$ vs *1xN/*1; $p<0.05$ vs *1xN/*4) (472, 497, 498) (Fig. 5). GPT activity was significantly higher in PMs (*4/*4) than in EMs (*1/*10, $p<0.05$) or IMs (*1/*4, *1/*5, $p<0.05$). The lowest GPT activity was found in EMs and IMs (472, 497, 498) (Fig. 6). Striking differences have been found in GGT activity between PMs (*4/*4), which showed the highest levels, and EMs (*1/*1, $p<0.05$; *1/*10, $p<0.05$), IMs (*1/*5, $p<0.05$), or UMs (*1xN/*1, $p<0.01$) (Fig. 7). Interesting enough, the *10/*10 genotype, with the lowest values of GOT and GPT, exhibited the second highest level of GGT after *4/*4, probably indicating that CYP2D6-related enzymes differentially regulate drug metabolism and transaminase activity in the liver. These results are also clear in demonstrating the direct effect of CYP2D6 variants on transaminase activity (472, 497, 498).

No clinical trials have been performed to date to elucidate the influence of CYP2D6 variants on the therapeutic outcome in AD in response to cholinesterase inhibitors or other anti-dementia drugs. To overcome this lack of pharmacogenetic information, we have performed the first prospective study in AD patients who received a combination therapy with (a) an endogenous nucleotide and choline donor, CDP-choline (500 mg/day), (b) a nootropic substance, piracetam (1600 mg/day), (c) a vasoactive compound, 1,6 dimethyl 8ß-(5-bromonicotinoyl-oxymethyl)-10a-methoxyergoline (nicergoline) (5 mg/day), and (d) a cholinesterase inhibitor, donepezil (5 mg/day), for one year. With this multifactorial therapeutic intervention, 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 one

CYP2D6-Related Therapeutic Response in Alzheimer's Disease



	Extensive Metabolizers		Intermediate Metabolizers						Poor Metabolizers		Ultra-rapid Metabolizers	
CYP2D6	*1/*1	*1/*10	*1/*3	*1/*4	*1/*5	*1/*6	*10/*10	*4/*10	*4/*4	*5/*5	*1xN/*1	*1xN/*4
N	43	7	2	11	3	2	2	1	7	1	3	3
Min	22,03	19,83	21,33	22,25	20,04	22,9	17,6	21	14,03	22	18,66	22,3
Max	24,92	22,64	27,51	24,5	21,7	24,92	18,6	22	18,31	23	23,14	23,9
Mean	23	21,22	24,79	23,25	20,87	23,72	18,15	21,5	16,52	22,5	21,1	23,07
SD	0,97	0,97	2,04	0,75	0,62	0,8	0,32	0,5	1,59	0,5	1,73	0,47
r	0,44	0,97	0,98	-0,26	0,7	0,93	-0,69	-0,87	-0,98	-0,87	-0,97	0,94
a Coef	22,1	19,27	20,65	23,67	19,96	22,17	18,61	22,4	19,72	23,4	24,55	22,15
b Coef	0,25	0,55	1,18	-0,11	0,25	0,44	-0,13	-0,25	-0,91	-0,25	-0,98	0,26

Figure 10. **CYP2D6-Related therapeutic response in Alzheimer's disease. Influence of CYP2D6 genotypes on cognitive performance during treatment with a multifactorial therapy. Adapted from Cacabelos (Ref. 497 & 498)**

year of treatment (Fig. 8-10). 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 (Fig. 10). 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 (472,497,498) (Fig. 10). The CYP2D6-related therapeutic responses can be modified by the presence of the APOE-4/4 genotype which converts EMs and IMs into poor responders (497,498) (Fig. 11).

From all these data we can conclude the following: (i) The most frequent CYP2D6 variants in the Spanish population are the *1/*1 (47.10%), *1/*4 (17.42%), *4/*4 (8.37%), *1/*10 (4.52%) and *1xN/*1 (4.52%), accounting for more than 80% of the population; (ii) the frequency of EMs, IMs, PMs, and UMs is about 51.61%, 32.26%, 9.03%, and 7.10%, respectively; (iii) EMs are more prevalent in AD (57.47%) than in controls (44.12%); IMs 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 is similar in AD (9.20%) and controls (8.82%); and UMs are more frequent among AD cases (8.04%) than in controls (5.88%); (iv) there is an accumulation of AD-related genes of risk in PMs and UMs; (v) PMs and UMs tend to show higher transaminase activities than EMs and IMs; (vi) 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; (vii) EMs and IMs can be converted into poor responders by the presence of the APOE-4/4 genotype (Fig. 11); (viii) 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 (12,13,497,498).

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 (e.g., 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 (12,13,188,192-194). 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 (468). Although most studies predict the safety of donepezil (480) and galantamine (81,86,481), as the two principal cholinesterase inhibitors metabolized by CYP2D6-related enzymes (86,482), 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 (67,79,483,484). 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 (485). Therefore, 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.

OPTIMIZATION OF ALZHEIMER'S DISEASE THERAPEUTICS

The optimization of AD therapeutics requires the establishment of new postulates regarding (a) the costs of medicines, (b) the assessment of protocols for global treatment in dementia, (c) the implementation of novel therapeutics addressing causative factors, and (d) the setting-up of pharmacogenetic/pharmacogenomic strategies for drug development (12,13,33,188,192-194).

The cost of medicines is a very important issue in many countries because of (i) the growing of the aging population (>5% disability), (ii) AD patients (5-15%>65 years) belong to an unproductive sector of the population with low income, and (iii) the high cost of health care systems in developed countries. Despite the effort of the pharmaceutical industry to demonstrate the benefits and cost-effectiveness of available drugs, the general impression in the medical community and in some governments is that the anti-dementia drugs present in the market are not cost-effective (14,15,159,164). Conventional drugs for AD are relatively simple (and some of them are also very old) compounds with unreasonable prices. There is an urgent need to assess the costs of new trials with pharmacogenetics and pharmacogenomics strategies, and to implement pharmacogenetic procedures to predict drug-related adverse events (50,424,425).

Cost-effectiveness analysis has been the most commonly applied framework for evaluating pharmacogenetics. Pharmacogenetic testing is potentially relevant to large populations that incur in high costs. For instance, the most commonly drugs metabolized by CYP2D6 account for 189 million prescriptions and US$12.8 billion annually in expenditures in the US, which represent 5-10% of total utilization and expenditures for outpatient prescription drugs (486). In performing pharmacogenomic studies in AD, it is necessary to rethink the therapeutic expectations of novel drugs, redesign the protocols for drug clinical trials, and incorporate biological markers as assessable parameters of efficacy and prevention (10,12,13,32,96,244,245,487). In addition to the characterization of genomic profiles, phenotypic profiling of responders and non-responders to conventional drugs is also important (and currently neglected). Brain imaging techniques, computerized electrophysiology,

and optical topography can help in the differentiation of responders and non-responders. For instance, brain mapping shows a good imaging correlation with APOE-related genotypes in AD patients (13), and responders and non-responders to donepezil have different EEG cortical rhythms (488). Age and AChE- and BuChE-related genotypes can also influence the therapeutic response to donepezil and rivastigmine (213). The early identification of predictive risks requires genomic screening and molecular diagnosis, and individualized preventive programs will only be achieved when pharmacogenomic/pharmacogenetic protocols are incorporated to the clinical armamentarium with powerful bioinformatics support (12,13).

Another important issue in AD therapeutics is that anti-dementia drugs should be effective in covering the clinical spectrum of dementia symptoms represented by memory deficits, behavioural changes, and functional decline (10,432). It is difficult (or impossible) that a single drug will be able to fulfil this criteria. A potential solution to this problem is the implementation of cost-effective, multifactorial (combination) treatments integrating several drugs, taking into consideration that traditional neuroleptics and novel antipsychotics (and many other psychotropics) deteriorate both cognitive and psychomotor functions in the elderly and may also increase the risk of stroke (432). Few studies with combination treatments have been reported and most of them are poorly designed. We have also to realize that the vast majority of dementia cases in people older than 75-80% are of a mixed type, in which the cerebrovascular component associated with neurodegeneration can not be therapeutically neglected (12,13,36,244,245,489). In most cases of dementia, the multifactorial (combination) therapy appears to be the most effective strategy (12,13,188). The combination of several drugs (neuroprotectants, vasoactive substances, AChEIs, metabolic supplementation) increases the direct costs (e.g., medication) by 5-10%, but in turn annual global costs are reduced by approximately 18-20% and the average survival rate increases by about 30% (from 8 to 12 years post-diagnosis) (Cacabelos et al, unpublished results).

There are major concerns regarding the validity of clinical trials in patients with sAD. Despite the questionable experience with memantine (490), similar strategies have been used to demonstrate the utility of donepezil in sAD (125). This kind of studies bears some important pitfalls, including (a) short duration (<1 yr), (b) institutionalized patients, (c) patients receiving many different types of drugs, (d) non-evaluated drug-drug interactions, (e) side-effects (e.g., hallucinations, gastrointestinal disorders) that may require the administration of additional medication, (f) lack of biological parameters demonstrating actual benefits, and (g) no cost-effectiveness assessment, among many other possibilities of technical criticism (12,13,491).

Major impact factors associated with drug efficacy and safety include the following: (i) the mechanisms of action of drugs, (ii) drug-specific adverse reactions, (iii) drug-drug interactions, (iv) nutritional factors, (v) vascular factors, (vi) social factors, and (vii) genomic factors (nutrigenetics, nutrigenomics, pharmacogenetics, pharmacogenomics). Among genomic factors, nutrigenetics/nutrigenomics and pharmacogenetics/pharmacogenomics account for more than 50-60% of efficacy-safety outcomes in current therapeutics (12,13).

Some authors consider that priority areas for pharmacogenetic research are to predict serious adverse reactions (ADRs) and to establish variation in efficacy (492). Both requirements are necessary in AD to cope with efficacy and safety issues associated with either current AD-related drugs and drugs in development. Since drug response is a complex trait, genome-wide approaches (oligonucleotide microarrays, proteomic profiling) may provide new insights into drug metabolism and drug response. Genome-wide family-based association studies, using single SNPs or haplotypes, can identify associations with genome-wide significance (493).

To achieve a mature discipline of pharmacogenetics and pharmacogenomics in CNS disorders and dementia it would be convenient to accelerate the following processes: (a) educate physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (b) standardize genetic testing for major categories of drugs; (c) validate pharmacogenetic and pharmacogenomic procedures according to drug category and pathology; (d) regulate ethical, social, and economic issues; and (e) incorporate pharmacogenetic and pharmacogenomic procedures to both drugs in development and drugs in the market to optimize therapeutics (12,13,494, 497). ■

Interaction of CYP2D6 and APOE in the Pharmacogenetics of Alzheimer's Disease

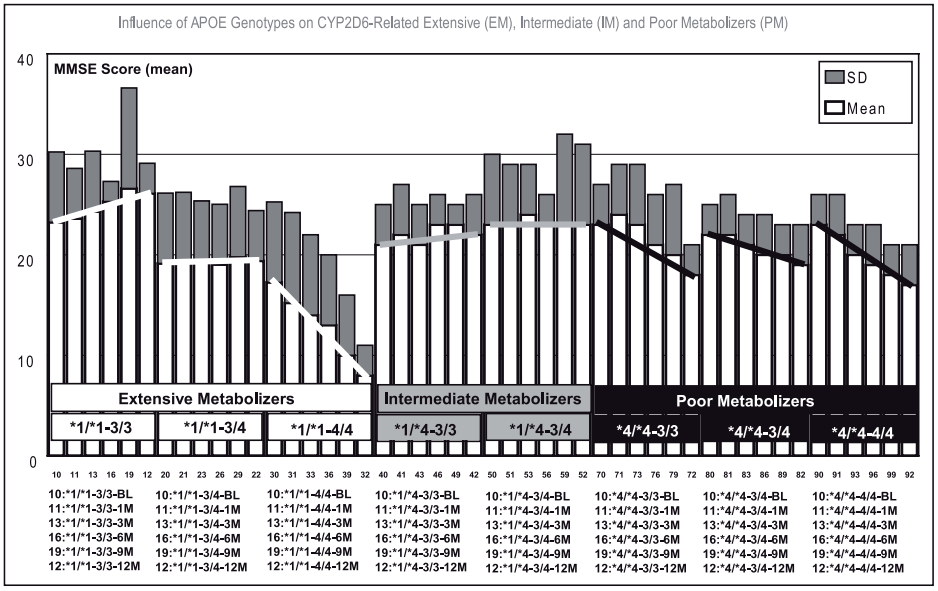


Figure 11. **Interaction of CYP2D6 and APOE in the pharmacogenetics of Alzheimer's disease. Adapted from Cacabelos (Ref. 497**

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 5). Main pharmacological properties of donepezil include the following (Tables 1): (i) after oral ingestion, peak plasma concentrations are achieved in 3-5 hours; (ii) absortion is not affected by food; (iii) linear pharmacokinetics over a dose range of 1-10 mg/day; (iv) steady-state plasma concentration reached in 14-21 days with daily dosing; (v) mean steady-state plasma concentrations are dose proportional; (vi) mean cerebral spinal fluid/plasma concentration is 0.157; (vii) 96% of circulating donepezil is protein bound; (viii) elimination half-life is approximately 70 hours; (ix) it is mostly excreted unchanged in urine; (x) there is some CYP3A4- and CYP2D6-related metabolism; (xi) there are not significant drug interactions; (xii) the most important ADRs associated with donepezil are body events (45%), cardiovascular (18%), digestive (34%), haematic 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); (xiii) donepezil is effective in mAD and sAD cases showing a modest improvement in cognition, behaviour, and function (Table 2); (xiv) the effects of donepezil are dose-dependent, with optimal effects in the range of 5-10 mg/day; and (xv) due to its pharmacological properties donepezil has been used in other CNS disorders with uncertain effects (Table 7).

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: (i) 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; (ii) pharmacokinetic and pharmacodynamic weaknesses of the AChEIs; (iii) 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; (iv) critical problems of patient recruitment not differentiating pure AD cases from cases of AD with cerebrovascular component and/or other medical conditions; (v) differences in the genetic profile of AD patients who exhibit a genotype-related therapeutic response (pharmacogenomics; efficacy issues); and (vi) pharmacogenetic problems associated 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 (i.e., anti-oxidation, inhibition of neuronal excitotocity-related mechanisms, cerebrovascular regulation, etc).

Some other conclusions can also be drawn, such as: (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 switch 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 (498). ■

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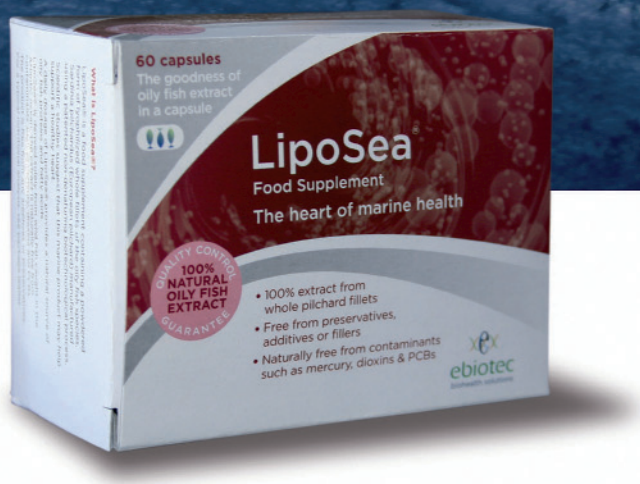

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