Galantamine for Alzheimer's Disease and Alzheimer's Disease with Cerebrovascular Disease

3

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3.1 Introduction

Despite numerous attempts to develop new classes of compounds for either the progression or symptomatic treatment of Alzheimer's disease, there have been no successes to date. Hence, the mainstay of the treatment of mild-to-moderate Alzheimer's disease (AD) remains the cholinesterase inhibitors. Despite the widespread use of these drugs, there is scant literature discussing the relative differences among these compounds and the practical consequences of those differences. Indeed, a recent review in a respected journal notes that "AD … responds only marginally and briefly to currently available drugs" (Bloom 2014). The purpose of this review article is to delineate the important properties that distinguish these compounds and the clinical implications of those differences. It will do so by largely focusing on donepezil, the most frequently prescribed cholinesterase inhibitor, and contrasting donepezil with galantamine, the cholinesterase inhibitor that differs the most in its mechanism of action within this class of compounds.

Two key properties differentiate donepezil and galantamine. These properties are the drugs' interaction with nicotinic receptors and their half-lives. Galantamine has been shown to be a positive allosteric modulator of nicotinic receptors, a property not shared by donepezil (Samochocki et al. 2003). Galantamine has a half-life of 7–8 h (Product Monograph 2008). In contrast, donepezil's half-life in the elderly is approximately 104 h (Ohnishi et al. 1993). The consequences of continuous, as compared to physiologically timed cholinesterase inhibition, will be addressed below.

3.2 Nicotinic Enhancement

Galantamine's enhancement of nicotinic receptors is especially pronounced at the $\alpha_4\beta_2\alpha_5$ receptor (Kuryatov et al. 2008). Galantamine potentiates depolarization of $\alpha_4\beta_2$ nicotinic receptors in human embryonic kidney-263 cells (Samochocki et al. 2003). That effect is blocked by FK-1, an antibody that specifically binds the

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Table 3.1 Incidence of diarrhea in controlled clinical trials of cholinesterase inhibitors cited in 2002 Physicians' Desk Reference (PDR)

Drug (dose)	PDR page #	Total *n*		% with diarrhea		% drug–% placebo (%)
		Drug	Placebo	Drug (%)	Placebo (%)	
Tacrine (40–160 mg)	1354	634	342	16	5	11
Galantamine (16–24 mg)	1796	1040	801	9	7	2
Rivastigmine (6–12 mg)	2344	1189	868	19	11	8
Donepezil (5–10 mg)[a]	2666	747	355	10	5	5

[a]3 % discontinuation rate for diarrhea in patients taking 10 mg/day (page 2666)

galantamine positive allosteric modulatory site on nicotinic receptors. Galantamine has a similar effect on α_7 receptors in xenopus oocytes (Texido et al. 2005). Donepezil does not enhance the activity of nicotinic receptors beyond the effect of acetylcholinesterase inhibition. This difference suggests that galantamine should have a profile with more nicotinic activity than does donepezil. Conversely, donepezil should have a profile that favors more muscarinic activity than does galantamine. These differences, in nicotinic stimulation, and those in duration of action, to be discussed later, have profound clinical implications that are just being recognized.

3.2.1 Peripheral Cholinergic Effects

One simple way to differentiate nicotinic and muscarinic clinical effects is the relative incidence of diarrhea, as diarrhea is a reflection of muscarinic activity. The large, double-blind, placebo-controlled registration studies reported in the Physician's Desk Reference indicate that the relative difference in the incidence of diarrhea between patients on rivastigmine or donepezil compared to placebo is large. Donepezil patients reported diarrhea 100 % more frequently than placebo patients (Medical Economics Staff 2002). In contrast, galantamine patients had only 29 % more diarrhea than their placebo counterparts. Table 3.1 summarizes these differences.

3.2.2 Cognitive Profile

The cognitive profiles of galantamine and donepezil demonstrate a difference that can be attributed to enhanced nicotinic stimulation by galantamine. A 52-week, rater-blinded study directly compared the effects of donepezil and galantamine on the Mini-Mental State Exam (MMSE) and the Alzheimer's Disease Assessment Scale—cognitive (ADAS-cog) (Wilcock et al. 2003). In a preplanned analysis of patients meeting the UK's National Institute of Clinical Excellence criteria for moderate AD (having MMSE scores from 10 to 18), the two drugs significantly differed in their ability to improve performance on the attention and language subscales over

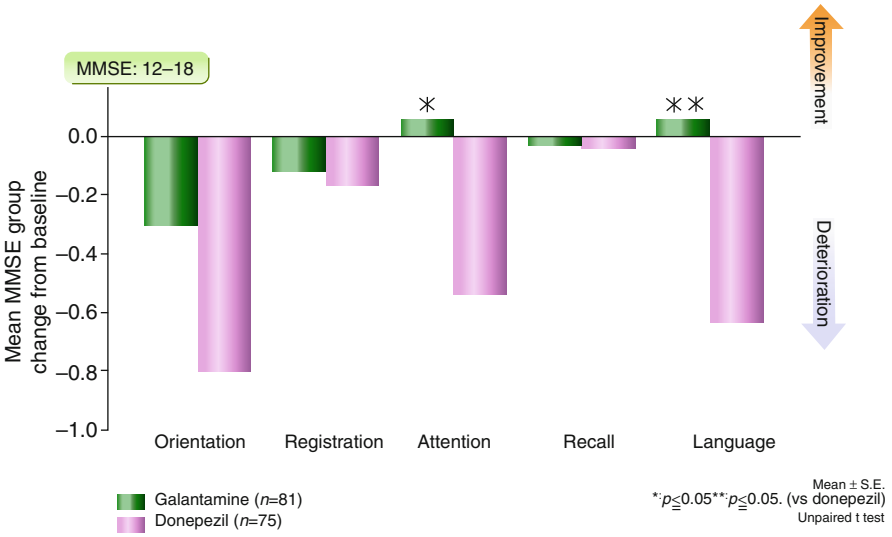

Fig. 3.1 Galantamine patients scored significantly better than donepezil patients on MMSE (Mini-Mental State Exam) subscales requiring attention and working memory, both of which involve nicotinic mechanisms. The drugs were compared in a randomized, 1-year, rater-blinded study in patients with MMSE scores of 12–18. *MMSE* Mini-Mental State Exam (Wilcock et al. 2003)

the 52 weeks of the study, as shown in Fig. 3.1. The language subscale contains commands, which require working memory. Both attention and working memory can be enhanced by nicotinic stimulation. On the ADAS-cog, performance on the "commands" question was also significantly better in galantamine than donepezil patients (data on file). This pattern of results with galantamine is consistent with its ability to enhance central nicotinic activity beyond cholinesterase inhibition, through allosteric modulation of receptors.

3.2.3 Neuroprotection

As the experimental therapeutics of AD has evolved, increased emphasis has been placed on the development of compounds that would offer neuroprotection, enhance the clearance of β-amyloid (Aβ), or decrease the formation or toxicity of various forms of the Aβ peptides. Nicotinic activity can mediate both neuronal survival and Aβ clearance. That nicotinic mechanisms may be neuroprotective has strong epidemiologic support in a preventive effect of smoking on the incidence of Parkinson's disease. There is a beneficial effect of duration of smoking, and neuroprotection has been demonstrated in identical twins discordant for smoking (Chen et al. 2010). While lifestyle and many other physiological effects of smoking may contribute to these findings, the $\alpha_4\beta_2$ and a_7 nicotinic receptors can mediate neuroprotective mechanisms (Kawamata and Shimohama 2011). Smoking itself does not lower the incidence of AD, perhaps due to adverse effects on other organ systems (Kulkull 2001).

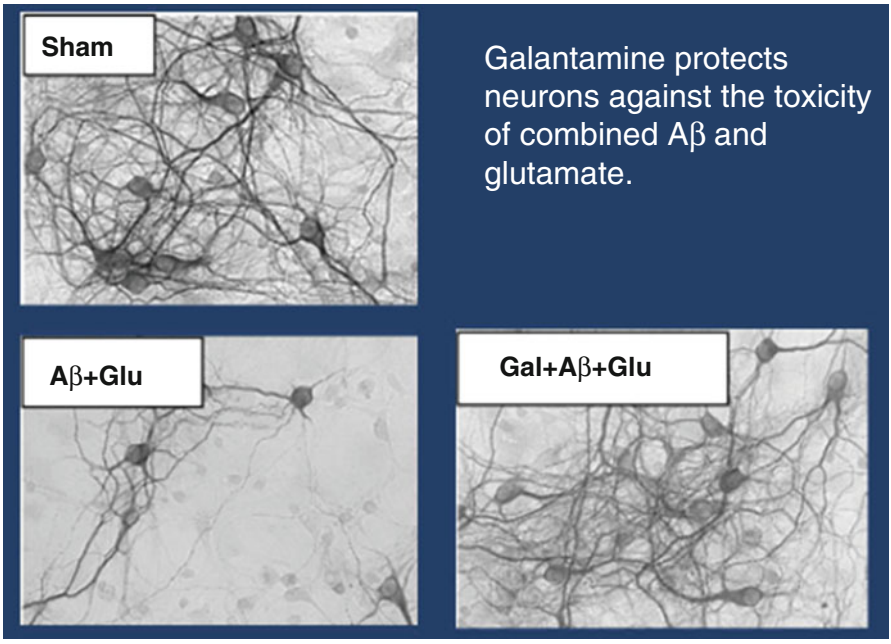

Fig. 3.2 Galantamine exerts a protective effect against β-amyloid (Aβ)-enhanced glutamate cytotoxicity. Aβ, $A\beta_{1-40}$ (10.0 nM) + $A\beta_{1-42}$ (1.0 nM) 4 days; Glu, glutamate (20.0 μM) 24 h; Aβ + Glu, 4-day treatment with Aβ followed by 24-h treatment with glutamate; Gal, simultaneous treatment with galantamine and Aβ for 4 days (1.0 and 10.0 μM). Galantamine 1.0 and 10.0 μM significantly protected neurons against Aβ-enhanced glutamate neurotoxicity ($p < .01$) (Kihara et al. 2004)

Depending on brain region, 11–37 % of $\alpha_4\beta_2$ nicotinic receptors have as their fifth member, the α_5 subunit (Kuryatov et al. 2008). These $\alpha_4\beta_2\alpha_5$ subtypes are more sensitive to agonists and produce a larger maximal current than $\alpha_4\beta_2$ receptors lacking the α_5 subunit (Mao et al. 2008). Galantamine, at clinical concentrations, enhances the activity of $\alpha_4\beta_2\alpha_5$ receptors by 220 %, as compared to 20–30 % for other nicotinic receptors (Kuryatov et al. 2008). As shown in Fig. 3.2, galantamine, applied simultaneously with a combination of glutamate and Aβ species, blocks their neurotoxic effect (Kihara et al. 2004). In a separate experiment, 24-hour pretreatment of a neuronal culture with galantamine increased survival following a toxic dose of glutamate by 78 % ($p < .01$). The protection against glutamate was nicotinic, as mecamylamine blocked 2/3 of galantamine's benefit. Dihydrobetaerythroidine, an $\alpha_4\beta_2$-blocker, reduced the galantamine effect by a little more than half, while methyllyaconitine, an α_7-antagonist, caused a 1/3 reduction (all $p < .01$) (Takada-Takatori et al. 2006). Thus, galantamine's potent effect on an especially active subset of $\alpha_4\beta_2$ receptors may play a large part in galantamine-induced neuroprotection. Cholinesterase inhibitors which do not enhance nicotinic receptor function through allosteric enhancement may nevertheless be expected to have some nicotinic activity. Thus, donepezil can protect neurons against glutamate toxicity, but is 10× less potent than galantamine (Takada-Takatori et al. 2009).

3.2.4 Aβ Clearance

Nicotinic stimulation can also enhance Aβ clearance. This becomes particularly relevant in light of studies that indicate that the key abnormality in Alzheimer's disease of late-onset (LOAD) is the inability to adequately clear Aβ. When Aβ clearance was measured following the infusion of labelled leucine and cerebrospinal fluid (CSF) was sampled hourly, patients with LOAD were 30 % less efficient at clearing Aβ than controls (Mawuenyega et al. 2010). This finding took on increasing importance following a large study of brains from LOAD patients and controls. Bayesian analysis of the gene expression that differentiated these two groups indicated that upregulation of genes in the immune/microglial module in LOAD patients best differentiated them from controls. Gene expression in the immune/microglial module was most highly correlated with neuropathology traits such as frontal and parietal atrophy and ventricular enlargement. The authors note that alleles of genes found in genome-wide association studies to increase the risk of LOAD, such as CD33 and TREM2, also fall within the immune/microglial network. To further explore this finding, the central gene in the network, TYROBP, was overexpressed in microglial cells. This resulted in downregulation of 99 % of functional genes within the microglia, such as those involved in RNA metabolism and cell-cycle mitosis (Zhang et al. 2013). Microglia perform many functions which can variously exacerbate or attenuate the Alzheimer process. Microglial function may be impaired in LOAD patients.

The importance of the elucidation of a group of genes that influences immune modulation and microglial activity that differentiates LOAD patients from controls was underscored in an editorial discussing an experiment in which CD33, a microglial-surface protein increased in LOAD, inhibited Aβ clearance (Gandy and Heppner 2013). The editorial pointed out that microglia can exist in an inflammatory, harmful state, or an amyloid-clearing, helpful state and that "microglia-targeted therapies must be finely targeted." It noted that there were only two approved drugs that were known to increase the phagocytic activity of microglia, the PPARγ agonist pioglitazone and the mixed acetylcholinesterase inhibitor–nicotinic allosteric agonist galantamine (Takata et al. 2010). This property is illustrated in Fig. 3.3 which demonstrates galantamine's ability to promote Aβ clearance by interacting with its allosteric nicotinic modulatory site on microglia. The enhancement of Aβ clearance can be completely blocked by the antibody FK-1 which blocks the galantamine modulatory site on nicotinic receptors.

Amyloid deposits in the brains of APdE9 mice carrying amyloid precursor protein (APP) and presenilin 1 (PS1) mutations, control and galantamine treated, are shown in Fig. 3.4. The brain slice shown in the left panel was from a mouse treated with galantamine, 5 mg/kg/day for two months prior to sacrifice at 11 months, resulting in a significant reduction in amyloid deposits. Additionally, treated mice showed improved learning and spatial memory in the water maze test (Takata et al. 2010). A similar result has been reported for short-term donepezil treatment of APP/PS1 mice (Easton et al. 2013). A 10-day treatment of Tg2576 (APPswe) mice with galantamine increased synaptophysin levels, but did not reduce Aβ species (Unger et al. 2006). These data indicate that cholinesterase inhibitors may be able to influence amyloid deposition in animal models of familial Alzheimer's disease.

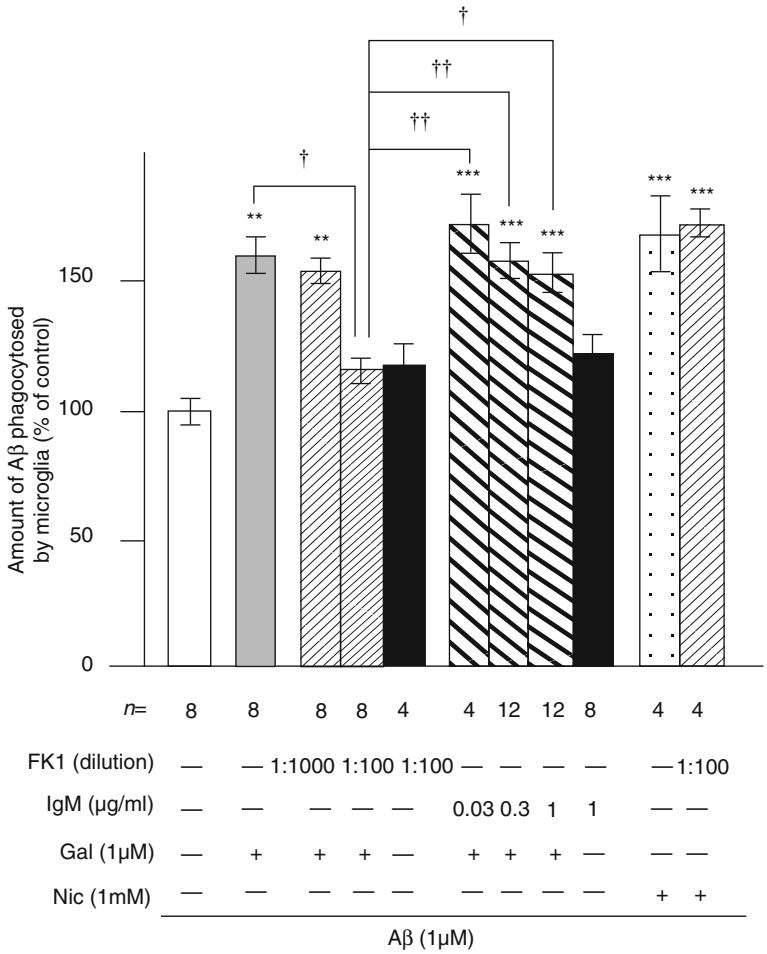

Fig. 3.3 Involvement of the APL-binding site for nAChRs in galantamine-enhanced microglial Aβ phagocytosis. Rat microglia were treated with 1 μM Aβ42 in the presence or absence of 1 μM galantamine or 1 mM nicotine. FK1 antibody or mouse IgM isotype control was added 10 min before treatment with Aβ42. The amounts of Aβ phagocytosed by microglia were measured by ELISA. **, $p < .01$; ***$p < .001$; versus Aβ42 alone. †, $p < 0.05$; ††, $p < 0.01$ versus Aβ42 plus galantamine and FK1 antibody (1:100). *FK1* FK1 antibody, *IgM* mouse IgM isotype control, *Gal* galantamine, *Nic* nicotine, *n* number of samples (Takata et al. 2010)

3.3 Human Clinical Data

3.3.1 Biomarkers

Changes in amyloid dynamics under the influence of galantamine have been shown in humans as well. CSF Aβ was measured in a 3-month head-to-head study of galantamine, donepezil, and rivastigmine in mild-to-moderate AD patients (Nordberg

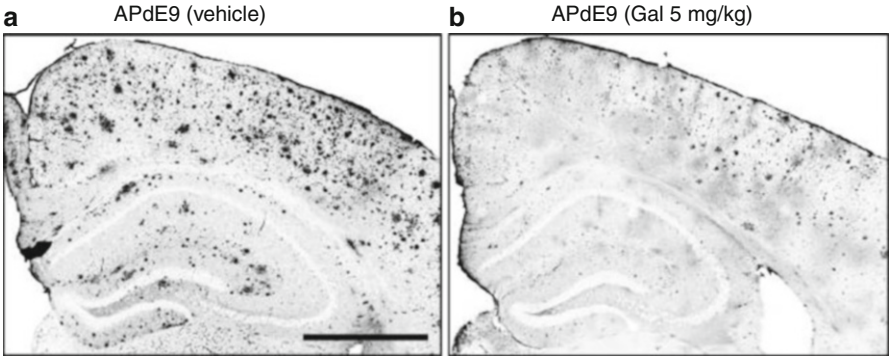

Fig. 3.4 Galantamine increased Aβ clearance in the brains of APdE9 mice. *A* and *B*, brain sections of vehicle-treated (**a**) or galantamine-treated (**b**) APdE9 mice were immunostained with anti-Aβ antibody. Mice were treated with 5 mg/kg daily of galantamine, or vehicle, for 2 months and sacrificed at 11 months. *Scale bar,* 500 μm (Takata et al. 2010)

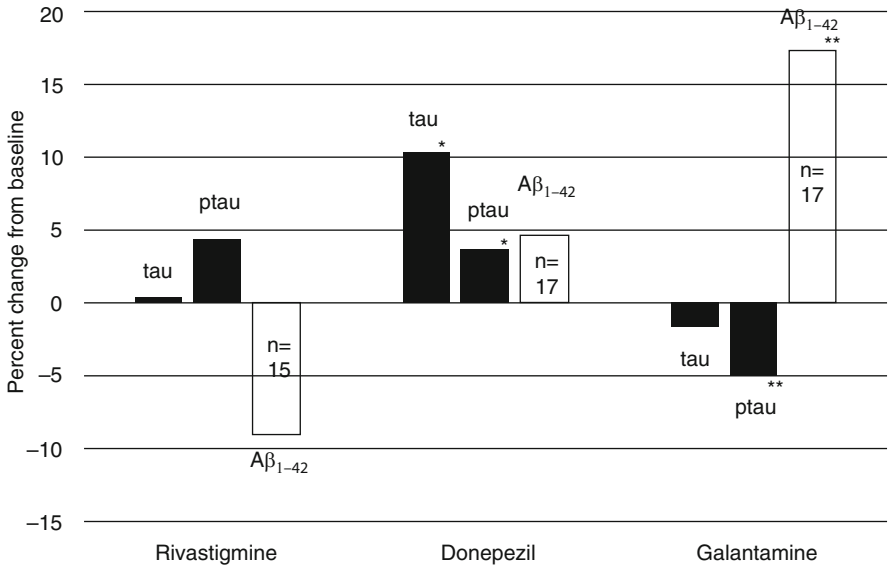

Fig. 3.5 Percent changes in CSF tau, ptau and $A\beta_{1-42}$ in patients completing 13 weeks of treatment with galantamine, donepezil, or rivastigmine; $*p<0.05$ *versus* baseline at 13 weeks, using one-way t-test; $**p<0.05$ *versus* rivastigmine, using an ANOVA model with treatment as the factor and baseline value as the covariate. *CSF* cerebrospinal fluid, *ptau* phosphotau (Data from Nordberg et al. 2009)

et al. 2009). Patients were randomized to each of the three drugs, and CSF was collected at baseline and endpoint and analyzed by personnel blinded to treatment and sample order. CSF $A\beta_{1-42}$ rose 17 % in galantamine patients, which was significantly different from the outcome in rivastigmine patients (Fig. 3.5). Figure 3.6 shows the CSF biomarker changes following treatment with the cholinesterase inhibitors in the

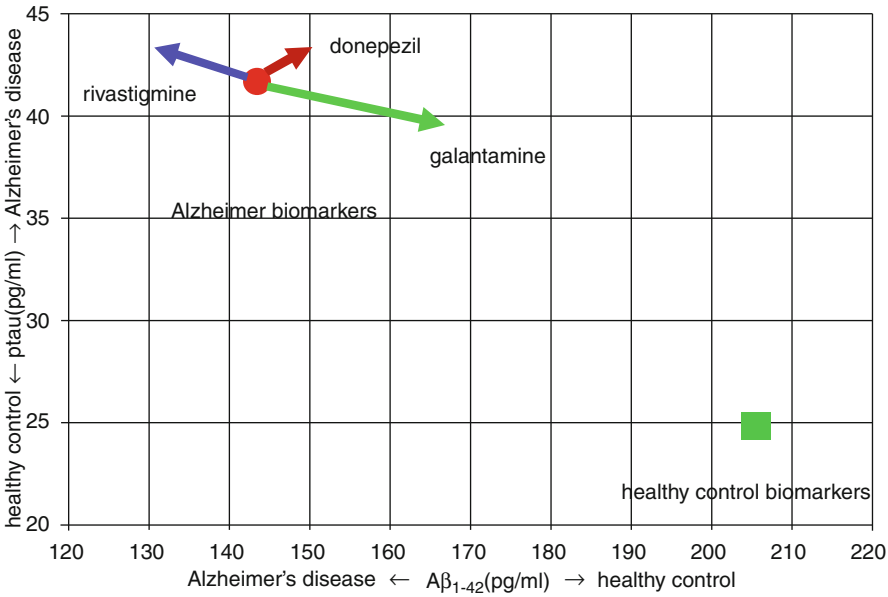

Fig. 3.6 Changes in CSF $A\beta_{1–42}$ and ptau following three months of rivastigmine, donepezil, or galantamine treatment of AD patients are shown in relation to average values for AD (*circle*) and healthy controls (*square*) from the ADNI database. Percentage changes from Nordberg et al. were applied to the ADNI baseline values. Significant differences in rivastigmine and galantamine effects on CSF $A\beta_{1–42}$ and ptau are apparent, as rivastigmine moves biomarkers away from healthy control values, while galantamine moves biomarkers towards those of control subjects (Data from Nordberg et al. (2009) and Okonkwo et al. (2010))

context of typical healthy control and Alzheimer values from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The percentage changes in baseline CSF $A\beta_{1–42}$ and phosphotau (ptau) which were reported by Nordberg et al. were applied to the mean CSF $A\beta_{1–42}$ and ptau values for AD patients from the ADNI database (Okonkwo et al. 2010). The statistically significant differences between rivastigmine and galantamine in CSF $A\beta_{1–42}$ and ptau are easily appreciated in Fig. 3.6, with rivastigmine moving biomarker values away from and galantamine moving $A\beta_{1–42}$ and ptau towards healthy control values. Numerous compounds have cleared amyloid from various mouse animal models and have not altered the progression of the Alzheimer process. Biomarkers of Alzheimer's disease still need further validation. The litmus test for whether any of these results has practical significance rests on clinical studies either in patients with AD or mild cognitive impairment (MCI). Since the average AD patient lives 8 years from the time of diagnosis, the most useful clinical studies are not the 6-month trials that have been used for registration purposes, rather they are trials of several years' duration. Three placebo-controlled, randomized studies have been carried out in patients with MCI that report the effect of acetylcholinesterase inhibitors on the MRI biomarker, global brain atrophy. Over the course of 29 months, global atrophy was not significantly diminished in

patients receiving donepezil compared to controls, nor was it at any time point in a four-year rivastigmine study (Jack et al. 2008; Feldman et al. 2007). In contrast, over 24 months MCI patients receiving galantamine had significantly less global atrophy than controls (Scheltens et al. 2004). It should be pointed out however that galantamine is not approved or recommended for patients with MCI (Winblad et al. 2008).

3.3.2 Mortality

Thus, the data from the 2-year MCI trial of galantamine combined with the biomarker data support the notion that galantamine has properties that are not shared with other cholinesterase inhibitors, that this effect is likely mediated by the stimulation of allosteric nicotinic receptors, and that it could involve neuroprotection and/or amyloid clearance. However, by far the most compelling data differentiating galantamine from the other compounds in this class comes from a recently concluded two-year, placebo-controlled, randomized trial of galantamine in AD patients (Hager et al. 2014). This study entered 2045 patients with AD or AD with cerebrovascular disease. Thirty-five percent of these patients were male, their average age was 73, and their average MMSE score was 19. The demographic and baseline characteristics of the placebo and galantamine groups were similar.

Before this study could be completed the Data Safety Monitoring Board halted the investigation because they had observed excess deaths in one arm of the study. Upon analysis it was determined that patients receiving placebo had a significantly higher mortality than patients receiving galantamine. Specifically, 56 deaths occurred in patients receiving placebo which was 5.5 % of that cohort. In contrast, there were 33 deaths in patients receiving galantamine, or 3.2 % of that cohort. The hazard ratio was .58, statistically significantly favoring galantamine ($p = .01$). The results are displayed in Fig. 3.7. The mortality benefit appears to increase with time.

Other large, double-blind, placebo-controlled studies of cholinesterase inhibitor administration to patients with mild-to-moderate Alzheimer's dementia which have been conducted for varying periods have reported mortality. Those studies have been collapsed by duration of treatment and are presented in Table 3.2 (Rogers et al. 1998a, b; Burns et al. 1999; Tariot et al. 2000, 2001; Winblad et al. 2001; Mohs et al. 2001; AD 2000 Collaborative Group 2000; Raskind et al. 2000; Rockwood et al. 2001; Erkinjuntti et al. 2002; Brodaty et al. 2005; Homma et al. 2011; Hager et al. 2014). The data indicate that for a duration of drug administration of 6 months or less, there is a numerical diminution in mortality for patients taking either donepezil or galantamine compared to placebo. However, by 1 year, the advantage of donepezil on mortality is lost, and, by 2 years, the death rate in patients randomized to donepezil is 27–31 % higher than those randomized to placebo or to rivastigmine (Bullock et al. 2005). In contrast, the relative death rate on galantamine as compared to placebo at 6 months is maintained at 2 years.

Mortality in severe and vascular dementias has been assessed in a number of 3–6-month studies. In three vascular dementia studies, 5–10 mg donepezil was administered to 1475 donepezil patients and 718 placebo patients. The mortality

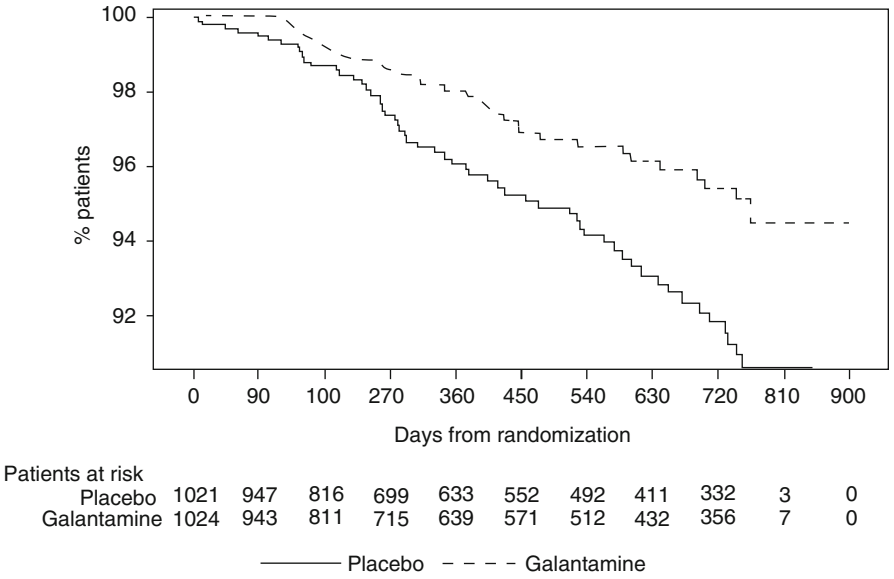

Fig. 3.7 Time from randomization to death (safety analysis set) (Hager et al. 2014)

Table 3.2 Mortality over time in double-blind, placebo-controlled, randomized trials in mild-to-moderate Alzheimer's dementia

	Donepezil			Galantamine		
	Donepezil deaths/*n*	Placebo deaths/*n*	Hazard ratio	Galantamine deaths/*n*	Placebo deaths/*n*	Hazard ratio
3–6 months	7/1274	11/693		24/2803	16/1334	
%	.55 %	1.59 %	0.35	.86 %	1.20 %	0.71
1 year	7/356	7/361				
%	1.97 %	1.94 %	1.01			
2 years	63/242	50/244		33/1024	56/1021	
%	26.0 %	20.5 %	1.27	3.22 %	5.49 %	0.59

rates were 1.6 % for drug, and 1.1 % for placebo, a ratio of 1.46 (Black et al. 2003; Wilkinson et al. 2003; Roman et al. 2010). In contrast, the mortality ratio during a galantamine vascular dementia study was 0.49, as 5/396 (1.3 %) of galantamine patients and 10/390 (2.6 %) of placebo patients died (Auchus et al. 2007). In moderate-to-severe AD dementia studies, deaths totalled 28/773 (3.6 %) in donepezil patients and 32/669 (4.8 %) in placebo patients, a ratio of 0.76 (Black et al. 2007; Homma et al. 2008; Feldman et al. 2001; Winblad et al. 2006; Howard et al. 2007). Galantamine significantly reduced mortality in its one study in severe dementia. Death occurred in 8/207 (3.9 %) galantamine and 21/200 (10.5 %) placebo patients, a ratio of 0.37 (Burns et al. 2009). Thus, short-term mortality in galantamine-treated

Table 3.3 Serious treatment-emergent adverse events[a] ≥2 %, hospitalizations, and deaths

	% incidence		% hospitalized		% death	
	pla	gal	pla	gal	pla	gal
Study totals	**12.0**	**12.6**	**8.6**	**11.0**	**4.6**	**3.0**
Nervous system (e.g., AD, stroke)	4.1	2.8	3.2	2.2	1.1	0.7
Cardiac (e.g., failure, myocardial infarction)	2.4	2.2	0.8	1.2	1.8	1.3
Infections, infestations (e.g., pneumonia)	1.5	2.0	0.6	1.7	0.5	0.4
Injury, poisoning, procedural complications	2.2	2.0	1.8	2.0	0.2	0.1

pla placebo, *gal* galantamine (data on file)

[a]Note these are fewer than all deaths, as the events preceding 11 deaths occurred >30 days from drug administration and thus were not treatment emergent

patients with dementias appeared to be favorably affected, which does not seem to be the case for donepezil use in vascular dementia.

In contrast to galantamine's favorable results in dementia populations, a 2-year study of 16–24 mg galantamine and a 3-year study of 10 mg donepezil in MCI patients showed drug/placebo mortality ratios greater than unity. The mortality ratio for galantamine at 2 years was 1.7 (34/1026, 3.3 %, of galantamine, and 20/1022, 2.0 %, of placebo patients) (Winblad et al. 2008). The risk appeared to be nominally greatest earlier in the study, as shown in Figure 5 of Winblad et al. 2008. In the 3-year donepezil study, 7/259 (2.7 %) of donepezil, 5/253 (2.0 %) of placebo, and 5/257 (1.9 %) of vitamin E patients died, a donepezil/placebo ratio of 1.35, similar to that of the 2-year donepezil trial in AD patients (Petersen et al. 2005). These drugs are not recommended for use in MCI.

Returning to the substantial mortality reduction in patients with mild-to-moderate AD, a 42 % decrease with galantamine at 2 years needs an explanation. Serious adverse events occurring during or within 30 days of treatment did not differ between galantamine (12.6 %) and placebo patients (12.0 %). The hospitalization rate for galantamine patients, however, was 11 %, as compared to 8.6 % for placebo patients. The largest categories of serious adverse events and their hospitalization and death rates are presented in Table 3.3. It is apparent that there was no diagnostic category containing at least 2 % of the treatment-related serious adverse events whose mortality was relatively more diminished than any other. However, patients on galantamine who had serious treatment-emergent symptoms, except for neurological symptoms including AD, were hospitalized more frequently, and died less frequently, than placebo patients. This raises the possibility that galantamine patients responded differently from placebo patients when a serious adverse event occurred. The cognitive and functional effects of galantamine therapy are presented below.

3.3.3 Cognitive and Functional Outcomes

The results of the MMSE over the course of this study are presented in Fig. 3.8. The last observation carried forward, intent-to-treat analysis shows a highly statistically

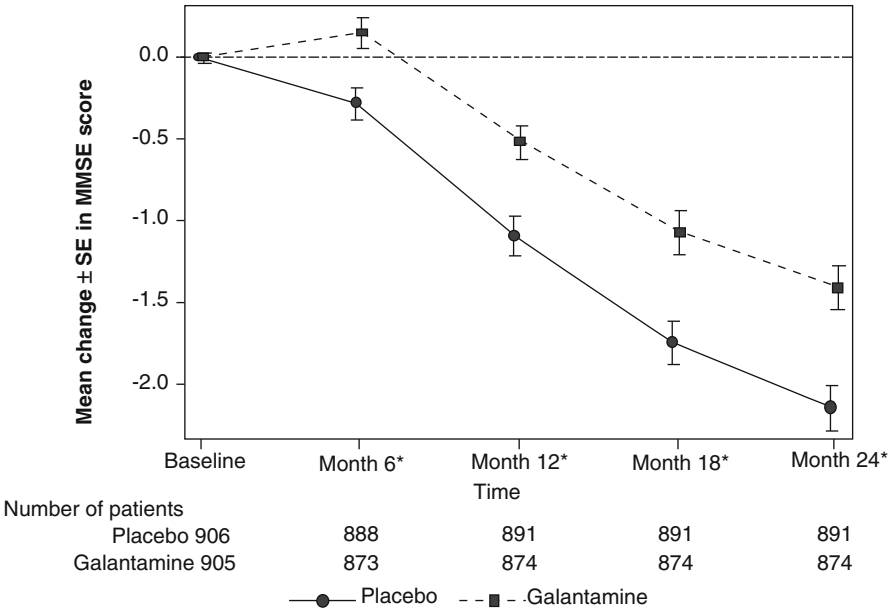

Fig. 3.8 Mean change in MMSE scores over time (LOCF) (ITT analysis set). *Significant difference between galantamine and placebo in MMSE score change from baseline. Estimates of treatment difference (95 % Cls) of MMSE using the repeated measures model (OC) were −0.48 (−0.73 to −0.22) at month 6, and −1.10 (−1.67 to −0.52) at month 24. *Cl* confidence interval, *ITT* intent-to-treat, *LOCF* last observation carried forward, *MMSE* Mini-Mental State Examination, *OC* observed case, *SE* standard error (Hager et al. 2014)

significant difference favoring galantamine over placebo at 6 and 24 months ($p < .001$). As measured by the Disability Assessment for Dementia (DAD), placebo patients took 17 months to reach the level of functional decline that galantamine patients experienced at 24 months. Mortality at 24 months in galantamine patients was at the level of placebo patients at 17 months as well. The MMSE and DAD subscales most affected by galantamine may offer insights into patients' abilities and behaviors. The MMSE domains, in intention-to-treat analysis, which most differentiated galantamine from placebo patients were orientation, attention, and language. (Attention and language are the same scales noted above to differ between galantamine and donepezil patients and to utilize nicotinic mechanisms.) In the language question, a patient must remember and follow a 3-stage command, read and execute "Close your eyes," and compose and write a sentence (Folstein et al. 1975). The DAD scales most significantly enhanced were basic and instrumental activities of daily living, initiation, effective performance, and planning and organization (data on file). The basic activities category includes eating, hygiene, and dressing, while telephoning, taking medications, and staying safely at home are instrumental activities (Gelinas and Gautier 1994). Initiation is the ability to decide or start an action appropriately. Effective performance is completing an action successfully. And planning and organization is essentially executive function—the ability to

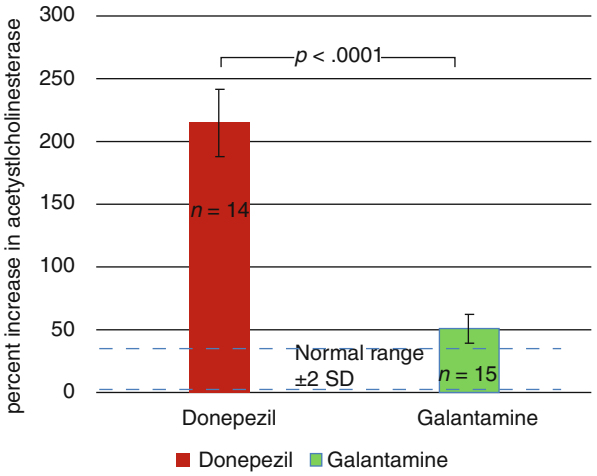

Fig. 3.9 Percent change in CSF acetylcholinesterase in patients completing 13 weeks of treatment with donepezil or galantamine. $p < 0.0001$, donepezil *versus* galantamine, using two-way *t*-test. *CSF* cerebrospinal fluid, *SD* standard deviation (Data from Nordberg et al. 2009)

structure an activity, obtain supplies, make decisions, and solve problems during its execution. One can begin to appreciate that this subset of skills, which is maintained to the greatest degree with galantamine therapy, might help a person maintain health and obtain and cooperate with help when it is needed. Thus, galantamine's ability to reduce cognitive and functional deterioration might have contributed to its mortality benefit.

3.3.4 Galantamine and Memantine

Some insight into a possible biological mechanism underlying the clinical results with galantamine is revealed by the subpopulation of patients who was receiving concomitant treatment with memantine along with either galantamine or placebo. An analysis of the MMSE scores at month 24 broken down by the concomitant use or nonuse of memantine reveals a surprising result as indicated in Fig. 3.9. Memantine use completely blocked galantamine's beneficial effect. It may simply be that memantine patients were sicker or unresponsive to cholinesterase inhibitors. Baseline MMSE values were significantly lower in memantine patients, by about a point. However, the decline of placebo-treated patients was similar whether or not memantine was taken. There is, however, a plausible pharmacological explanation. Memantine is an open-channel blocker of nicotinic receptors. Its distribution in the human brain is the same as that of the $\alpha_4\beta_2$-selective compound 5-[^{125}]-A-85380, being highest in the thalamus, followed by various cortical areas, with moderate binding in white matter (Ametamey et al. 2002; Pimlott et al. 2004). ^{18}F-memantine distribution did not correspond to that of TCP, an uncompetitive NMDA receptor blocker. Thus, memantine binding followed a nicotinic but not a glutamate-receptor pattern. Memantine blocks α_7 nicotinic receptors at an IC_{50} concentration of 5.1 μM and blocks $\alpha_4\beta_2$ nicotinic receptors at an IC_{50} of 7 μM (Aracava et al. 2005; Buisson

and Bertrand 1998). Memantine levels in plasma averaged 120 ng/ml during phase III studies in humans, about 0.67 μM (Periclou et al. 2006). Memantine partitions nearly 30× to brain tissue over plasma in rats (Saab and Roder 2011). Brain to plasma partitioning is similar in humans, as a 25:1 ratio was reached at the end of the PET study, at which time brain levels were still rising. All of these data taken together suggest that, in clinical use, memantine concentrations in brain tissue are well over 15 μM, blocking the nicotinic receptors whose function galantamine enhances. Thus, memantine negates galantamine's positive effect on the MMSE. This result would be consistent with an important role for nicotinic mechanisms in the cognitive effects of galantamine. The basic science therefore suggests that, in the clinic, galantamine may not have an effect in the presence of memantine, and this may be an inadvisable combination.

As previously noted, multi-year, double-blind, placebo-controlled studies of drugs approved for the treatment of AD are few, but highly relevant to the practicing clinician and to patients. The 2-year study of galantamine discussed above and the AD2000 collaborative study with donepezil are comparable studies that enrolled fairly similar populations, both including AD with or without concomitant cerebrovascular disease, used similar outcome measures, and included large numbers of patients, although AD2000 has been criticized for a high dropout rate. Thus, the outcomes of these studies offer some insight into the relative efficacy of these two drugs. In donepezil patients, functional and cognitive deterioration were each reduced by about 3 months over a 2-year period, compared to placebo. In contrast, galantamine reduced functional deterioration by 7 months, and cognitive deterioration by 9 months (11.4 months in patients not on memantine), in comparison to placebo.

Donepezil and rivastigmine have been compared in a large 2-year study (Bullock et al. 2005). Approximately 500 patients in each group contributed to the data analysis. This was a double-blind, randomized, controlled trial designed to evaluate the efficacy and tolerability of the two drugs, but did not contain a placebo control. There were no significant differences in cognitive or behavioral measures between the two drugs at the two-year time point.

3.3.5 Sleep Disturbance

Although the preclinical, cognitive, and mortality data outlined above might influence a clinician's decision on what drug to use in patients with AD, often those decisions are based on a drug's short-term adverse event profile. One side effect that is particularly problematic in patients with AD is insomnia. This problem is difficult for caregivers to cope with and, if severe, can lead to institutionalization as caregivers become exhausted. The incidence of insomnia for galantamine and donepezil across multiple pivotal studies is presented in Table 3.4 (Rogers et al. 1998a; Burns et al. 1999; Winblad et al. 2001; Mohs et al. 2001; Stahl et al. 2004). As can be seen from these comparisons, the incidence of insomnia in patients receiving galantamine over the initial period of

Table 3.4 Insomnia rates in pivotal clinical trials of donepezil and galantamine

Donepezil	Escalation to 10 mg/day (weeks)	Placebo		Donepezil 5 mg/day		Donepezil 10 mg/day	
		n	%	*n*	%	*n*	%
Rogers et al. (1998a)	1	153	5	157	8	158	18
Burns et al. (1999)	1	274	4	271	7	273	8
Winblad et al. (2001)	4	144	7	n/a	n/a	142	10
Mohs et al. (2001)	4	217	3	n/a	n/a	214	8

Galantamine	Escalation to 16–24 mg/day (weeks)	Placebo		Galantamine 8 mg b.i.d.		Galantamine 12 mg b.i.d.	
		n	%	*n*	%	*n*	%
Stahl et al. (2004)	2–8	714	2.2	279	1.1	705	2.6

treatment is markedly less than occurs with donepezil. Insomnia occurred in patients taking 5 mg donepezil at 1.6–1.8× the placebo rate, 2–3.6× more frequently in patients on 10 mg donepezil with a 1-week dose escalation, and 1.4–2.7× more frequently with a 4-week escalation. In contrast, insomnia in galantamine patients was half that in the placebo group at 16 mg and 1.2× the placebo rate at 24 mg. This was predictable, as normal brain acetylcholine levels fall markedly at night, and acetylcholinesterase activity rises, in order to permit sleep (Davis and Sadik 2006). Donepezil's multiple-day half-life greatly reduces the normal diurnal fluctuation of acetylcholinesterase activity (Tiseo et al. 1998). In response, acetylcholinesterase, as measured in CSF, increases dramatically in donepezil-treated patients, as will be discussed below.

Given the frequency of insomnia with donepezil treatment, it is not surprising that there is an increased use of hypnotics and other drugs that attempt to address this problem. Surveys of hypnotic administration in donepezil users as compared to nonusers show that the rate of hypnotic use among donepezil users was 2.65 times greater than in AD patients not taking donepezil (Stahl et al. 2003). In contrast, in patients participating in three double-blind clinical trials of galantamine, there was no significant difference in the use of sleep-promoting medications among placebo, 16 mg/day, and 24 mg/day patients, with percentages of 4.6, 2.9, and 5.6 %, respectively (Stahl et al. 2004). Thus, clinical observations are consistent with the basic science and confirm that donepezil interferes with sleep and is associated with hypnotic medication use.

Sleep disturbance in patients with AD is generally treated in one of two ways, with benzodiazepines and related compounds, or with neuroleptics. Both approaches are problematic. Hypnotics impair cognition, clearly a circumstance to be avoided in patients with AD, and neuroleptics impair cognition and are associated with increased mortality. Hence, the precipitation of sleep disturbance would seem an event to be avoided and would be a consideration when choosing among cholinesterase inhibitors.

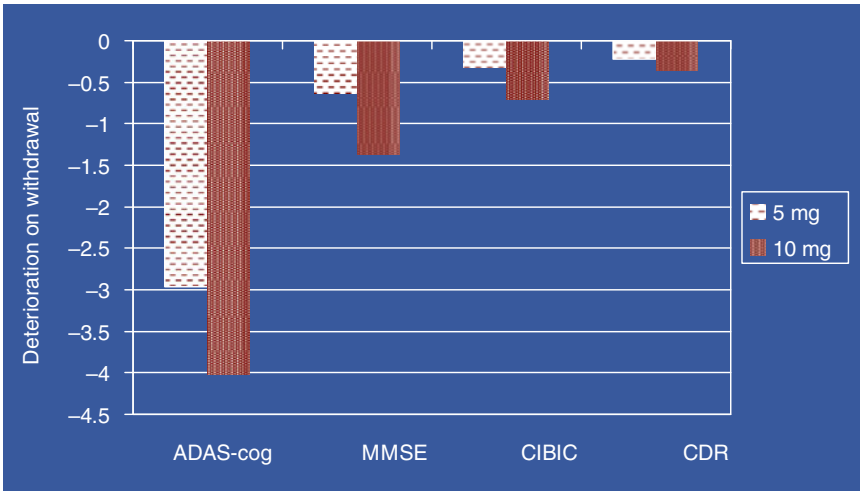

Fig. 3.10 A pattern of greater numerical decline in outcome measures is seen following 6 weeks of donepezil withdrawal from 10 mg as compared to 5 mg. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive, *MMSE* Mini-Mental State Exam, *CIBIC* Clinician's Interview-Based Impression of Change, *CDR* Clinical Dementia Rating (Data from Rogers et al. 1998a, b)

3.3.6 Cholinesterase Inhibitor Withdrawal

There is another subtle, but important way in which acetylcholinesterase inhibitors differ. Unlike the occurrence of insomnia and sleep disturbance, this difference and its consequences are rarely appreciated by the practitioner, but have been repeatedly demonstrated in blinded studies which evaluate patients throughout treatment and withdrawal. As mentioned above, cholinesterase inhibitors differ in their induction of acetylcholinesterase. Due to its prolonged half-life, leading to excessive cholinergic stimulation during the night, when acetylcholinesterase activity normally increases and acetylcholine release is very low, in order to permit sleep, donepezil induces marked elevations in CSF acetylcholinesterase protein. In contrast, galantamine produces modest changes. Rivastigmine changes are underestimated because rivastigmine's active metabolite does not leave the acetylcholinesterase binding site for acetylcholine, which blocks measurement of the acetylcholinesterase molecules to which rivastigmine is bound. The effects of 3 months of treatment of Alzheimer's patients with donepezil or galantamine, in a head-to-head study, on CSF acetylcholinesterase, are depicted in Fig. 3.10 (Nordberg et al. 2009). Donepezil, 10 mg, raised CSF acetylcholinesterase 215 %, while galantamine caused a 51 % increase, raising the lowered CSF acetylcholinesterase seen in AD to just above the normal range. A separate study evaluated CSF acetylcholinesterase concentrations before and after treatment of patients with 5 mg as compared to 10 mg donepezil per day for 6 months to a year. Patients on 10 mg donepezil had significantly greater increases in CSF acetylcholinesterase than patients on 5 mg ($p < .02$) (Davidsson et al. 2001). Not surprisingly, and likely as a consequence of the induction of

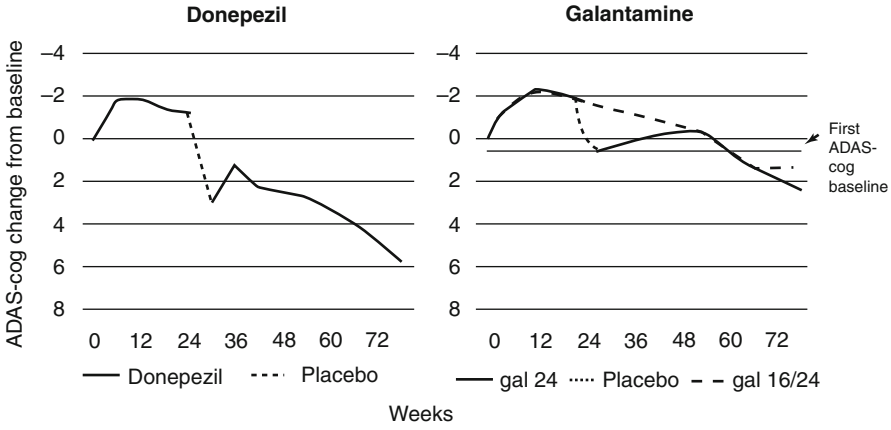

Fig. 3.11 ADAS-cog scores before, during, and after 6-week withdrawals in separate studies of donepezil and galantamine. Donepezil withdrawal caused a fall in scores below the first ADAS-cog, at baseline, which was partially restored by retreatment. Galantamine patients did not decline below the level of their first ADAS-cog (at screening). Retreatment completely restored galantamine patients' scores to those of patients treated continuously, with 16 mg/day, and increased to 24 mg/day at 24 weeks. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive, *gal* galantamine (Adapted from Doody et al. (2001), and from data on file)

acetylcholinesterase, a PET study of brain acetylcholinesterase inhibition in humans found no increase in enzyme inhibition in cortex when patients receiving 5 mg donepezil were raised to 10 mg/day (Kuhl et al. 2000). Increasing the donepezil dose apparently induces more acetylcholinesterase. With a much greater amount of enzyme to inhibit, 10 mg donepezil does not produce significantly more inhibition than 5 mg donepezil.

What might be the consequences of very large increases in brain acetylcholinesterase? This is classic pharmacologic tolerance. Thus, a decrease in the drug's effect with time and an exacerbation of symptoms upon withdrawal are expected. The greater the system's adaptation to the drug, in this case, the increase in acetylcholinesterase, the more severe the withdrawal would be expected to be. This is exactly the case with donepezil. Scores on four major outcome measures, ADAS-cog, MMSE, Clinician's Interview-Based Impression of Change, and Clinical Dementia Rating—Sum of Boxes, were nearly identical at the point of donepezil withdrawal in patients on 5 and 10 mg doses, yet the pattern of withdrawal decline was greater in patients having been on 10 mg than on 5 mg for all of these measures (Rogers et al. 1998a) (Fig. 3.11). Nevertheless, it would be expected that upon retreatment, acetylcholine levels would return to those previously achieved during treatment, and patients' performance would be restored. This did not happen. Clinical deterioration following donepezil withdrawal was not completely reversed by retreatment in the open-label phase following initial pivotal double-blind studies, as shown on the left side of Fig. 3.12. According to the investigators, discontinuation of donepezil for 6 weeks and restarting the drug "might not result in patients returning to the

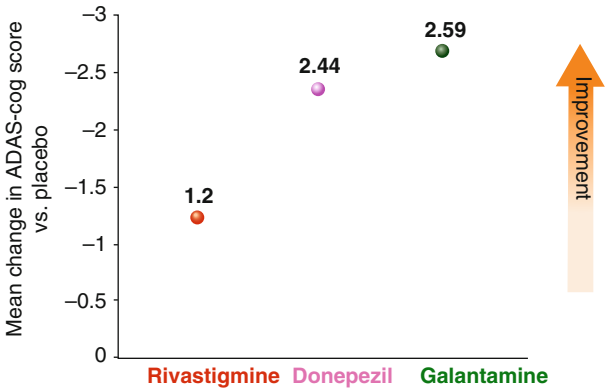

Fig. 3.12 ADAS-cog changes with cholinesterase inhibitors in Japanese phase III 6-month clinical trials in mild-to-moderate Alzheimer's patients. Short-term outcomes with donepezil and galantamine are similar. *ADAS-cog* Alzheimer's Disease Assessment Scale—cognitive (Data from Nakamura et al. (2011), Homma et al. (2008, 2011))

levels of cognition and global function that had been attained before interruption, taking into account the deterioration expected with the passage of time" (Doody et al. 2001). (These observations raise questions about the 23-mg dose of donepezil. The increased dose might be predicted to further increase counter-regulatory acetylcholinesterase production and the withdrawal consequences.) In contrast, galantamine patients withdrawn for 6 weeks return to the cognitive performance of patients who were treated continuously when they enter open-label retreatment, as shown on the right side of Fig. 3.12. Furthermore, unlike donepezil patients, withdrawn galantamine patients' ADAS-cog scores do not decline below the level of their first ADAS-cog, which had been performed at the screening visit, 7 months earlier (Tariot et al. 2000). (The first ADAS-cog in the donepezil study had been at baseline, 5.5 months earlier.) Rogers et al. (1998a). Thus, the irreversible component of withdrawal deterioration in donepezil patients does not occur with galantamine withdrawal.

To further elucidate the withdrawal and retreatment issues associated with donepezil, a study investigating donepezil washout and readministration was performed (Johannsen et al. 2006). Of 812 patients initiating treatment with donepezil open label, 619 remained after 12–24 weeks, 193 of whom did not show cognitive or behavioral benefit. These non-responding patients were randomized to continued donepezil or placebo for 12 weeks, and then donepezil therapy was reinstituted, single blind, for an additional 12 weeks. Behavioral measures during retreatment showed a surprising result. Deterioration on the neuropsychiatric inventory during the placebo phase was not restored by retreatment—the difference between continuously-treated and withdrawn patients was "largely preserved" during retreatment. However, "the difference in DAD scores increased slightly, as the placebo/donepezil group continued to decline further compared with the relative stability

observed in the continuous donepezil treatment group." The deterioration in activities of daily living which had begun during donepezil withdrawal did not abate when donepezil was readministered. The authors note that patients who had been randomized to placebo, when rechallenged with donepezil, "continued to fare worse than those who received continuous donepezil treatment, especially in measures of behavior." They go on to advise that "discontinuing therapy has implications for the caregiver and economic consequences for society" and recommend that "continuous persistent treatment may therefore be the most attractive option."

Realistically, AD patients will discontinue their drug therapy. In a California MediCal registry of 17,742 patients, 67.3 % of 15,128 donepezil and 60.1 % of 2614 rivastigmine patients had discontinued their drug by 431 days (Singh et al. 2005). Hence the persistent behavioral loss and the continued functional deterioration that follow donepezil withdrawal of patients who are not benefitting are adverse events which are not apparent during early dosing, but may be expected nonetheless. The relative ease of initiation of donepezil therapy may be explained by a concomitant rise in acetylcholinesterase, thus limiting early side effects. This same effort on the part of the brain to counteract donepezil's overriding the normal increase in acetylcholinesterase activity during the night is a plausible explanation for its withdrawal phenomena. To avoid donepezil withdrawal, one must avoid donepezil initiation.

There is a biological basis that may explain why patients restarted on donepezil after withdrawal do not achieve their previous levels of function and cognition, even adjusting for disease progression over time. One would expect the same dose of donepezil to restore synaptic acetylcholine to the levels achieved during the pre-withdrawal treatment and for patients to return to expected levels of performance. That they do not suggests that an underlying deterioration may have occurred. Data derived from APP transgenic mice who have had an additional gene for acetylcholinesterase inserted in their genome are an animal model of Alzheimer's disease with the superimposition of increased acetylcholinesterase protein, as occurs to a marked degree with 10 mg donepezil treatment. These animals show significantly increased frequency, burden, and density of amyloid plaques compared to controls with normal acetylcholinesterase, and these changes are apparent as early as 6 months of age (Rees et al. 2003). There are many components of amyloid plaques. Among these components are acetylcholinesterase, which can seed Aβ aggregation (Inestrosa et al. 1996). Thus, it could be anticipated that a multifold induction of acetylcholinesterase enzyme might accelerate the progression of Alzheimer pathology and the formation of toxic oligomers during withdrawal, as is consistent with the deterioration seen during with donepezil discontinuation and the irreversible component of the functional loss.

3.3.7 Tau

Tau is a marker of neuronal degeneration, and phosphotau (ptau), a more specific marker of AD, represents neurofibrillary tangles. CSF tau comes from axonal tau and is believed to represent axonal degeneration. CSF tau levels were significantly

related to levels of neurofilament light, which is an index of subcortical axonal damage, in a large CSF series (Skillback et al. 2013). A significant correlation between CSF tau and acetylcholinesterase protein, as well as between ptau and acetylcholinesterase protein, was found in patients treated with donepezil, 10 mg, for 6–12 months (Vanmechelen et al. 2001). These correlations are consistent with significant increases from baseline in all three biomarkers, acetylcholinesterase protein, tau, and ptau in CSF, after 3 months' treatment with donepezil, 10 mg, as shown in Figs. 3.5 and 3.9 (Nordberg et al. 2009). While tau is a predictor of MCI to AD conversion, a relationship of CSF tau with subsequent decline in AD patients has been found in single-center clinics with long follow-up, but not in the widely dispersed, multicenter Alzheimer's Disease Neuroimaging Initiative population, despite similar numbers of patients (for a review, see Gunnarrson et al.2014). A retrospective study of 72 mild AD patients, followed for a median of 6 years at Uppsala University, found a 5× risk of MMSE decline over 4 points/year in patients in the upper as compared to the lower half of the tau distribution (Gunnarsson et al. 2014). One hundred fifty-one AD patients were followed for 2.0 (1.0–5.0) years at VU University in the Netherlands. Patients with baseline tau in the lowest quintile declined by 1.6 MMSE points per year, as compared to 2.8 points for the highest quintile (Kester et al. 2009). Clinic patients with very elevated tau at Malmo University Hospital had poor cognitive performance at baseline and rapid deterioration over 3 years (Wallin et al. 2010). In contrast, the ADNI analyses, coming from 57 sites dispersed across the USA and Canada, and using different statistical methods, do not show these outcomes. Given the increases in acetylcholinesterase, which is counter-therapeutic, and tau and ptau, predictors of the activity of the Alzheimer process, present at 3 months of donepezil therapy, it is of interest to examine the long-term outcome of these patients.

3.3.8 Long-Term Outcomes in MCI

The longest randomized, placebo-controlled experience with donepezil is a 3-year study in amnestic MCI (Petersen et al. 2005). Multiple outcome measures during this study showed significant differences from baseline in the drug group, as compared with the placebo group until, with one exception, the 18-month time point. Subsequently, the advantages shown by treated patients diminished, until at 3 years, scores were similar in donepezil and placebo patients. Whereas during the first 12 months of treatment the conversion rate to AD from MCI was halved, by month 36 of treatment more than twice as many patients receiving donepezil were converting to AD than were patients receiving placebo (Petersen et al. 2004). In contrast, over a 24-month period of treatment with galantamine the ratio of galantamine to placebo patients converting to AD remained relatively steady between .69 and .83, not a statistically significant reduction (Winblad et al. 2008). As previously noted, galantamine is not approved or recommended for the treatment of MCI. Similar observations have been made regarding the ability of these two drugs to show beneficial effects on structural atrophy in MRI studies. Short donepezil studies reduce atrophy of brain structures on MRI, but these effects disappear in studies longer than 1

Table 3.5 Effects of cholinesterase inhibitors on brain structures as a function of years of treatment

Drug	Study	Time (years)	*n* drug/*n* placebo	Stage of AD/MCI	Hippocampus	Whole brain
Donepezil	Krishnan et al. (2003)	.5	34/44	MMSE 19	[a]	
	Schuff et al. (2011)	1.0	125/105	MMSE 28 CDR 0.5	ns	[a,b]
	Dubois et al. (2012)	1.0	113/109	CDR 0.5	[a]	[a]
	Hashimoto et al. (2005)	1.0	54/93	MMSE 22	[a]	
	Wang et al. (2010)	1.5	18/18	MMSE 25 CDR 0.5	ns	
	Jack et al. (2008)	2.5	37/54	MMSE 28 CDR 0.5	ns	ns
Galantamine	Scheltens et al. (2004)	2.0	142/127	CDR 0.5	ns	[a]

ns no significant effect
[a]Significant beneficial effect
[b]Post-hoc analysis

year. In contrast, galantamine significantly reduced global atrophy in MCI patients at 24 months (Table 3.5) (Krishnan et al. 2003; Schuff et al. 2011; Dubois et al. 2012; Hashimoto et al. 2005; Wang et al. 2010; Jack et al. 2008; Scheltens et al. 2004).

This review of acetylcholinesterase inhibitors indicates that donepezil and galantamine are not equivalent compounds for long-term treatment. Although recently concluded phase III clinical trials in Japan indicate approximate equivalence for these drugs at the 6-month point, donepezil does not maintain its effects on performance, brain structures, or mortality in the long-term, and its withdrawal includes an element of irreversible deterioration (Nakamura et al. 2011; Homma et al. 2008, 2011) Over 1 year, a head-to-head, rater-blinded study of galantamine versus donepezil demonstrated superiority for galantamine in responder rates and MMSE change from baseline (Wilcock et al. 2003). What this review has attempted to make clear is that these drugs differ substantially in the period beyond 1 year; in mortality, withdrawal, and course; and in their early effects on insomnia and its treatment. These differences have practical implications for the clinician and patients and lead to the conclusion that a superiority for galantamine in the long term is becoming apparent. Hence, the question arises as to the best approach for switching patients to galantamine from donepezil.

3.3.9 Switch Studies

There have been several donepezil to galantamine switch studies. Patients who wished to discontinue donepezil for reasons of efficacy, intolerance, or who wanted to try galantamine have participated in protocols with various washout periods and galantamine titration regimens (Rasmusen et al. 2001; Wilkinson et al. 2005;

Engedal et al. 2012; Sasaki and Horie 2014). Ninety-three to ninety-seven percent of these patients were successfully switched to galantamine, regardless of protocol. Cognitive and functional status were either maintained or improved by the end of dose escalation, in marked contrast to the steep deterioration of cognition and function which follows donepezil withdrawal. Side effects, primarily gastrointestinal, were lower during switching than when naïve patients were treated with comparable regimens. Washouts of 0–7 days have been used, with immediate, weekly, and monthly dose escalation. One protocol followed in Japan successfully transitioned patients taking donepezil 5, 8, or 10 mg a day to galantamine 16, 20, or 24 mg a day, respectively, using an immediate switch. Forty-four of forty-six patients successfully switched; the two who did not suffered from overexcitement and anorexia (Sasaki and Horie 2014). Delusions, agitation, and aberrant motor activity were significantly improved compared to donepezil treatment in AD patients ($p < .05$). Prolonged washouts may involve deterioration due to donepezil withdrawal and are not recommended, except in cases of donepezil intolerance, in which case 7–14 days' washout should be implemented (Farlow and Cummings 2007). As with all medications, clinical judgment will guide therapy.

Despite the large number of studies which have been reviewed in this paper, there is a strong clinical lore that surrounds this class of drugs. They are thought to have modest efficacy which decreases with time. This impression is probably driven by donepezil, the most-used cholinesterase inhibitor, which is easy to start and administer due to low side effects and long half-life, but loses efficacy and is damaging to discontinue to the extent that sponsored publications repeatedly caution against it. The large, controlled, 2-year galantamine trial in patients with AD and AD with cerebrovascular disease shows no loss of efficacy over 2 years. The final table in the review, Table 3.6, sets the galantamine data in the context of 2-year donepezil data and 18-month data from a compound recently developed to alter the course of AD, solanezumab (Prnewswire.com 2012). In long-term, placebo-controlled studies, galantamine increased survival and preserved cognition,

Table 3.6 Long-term, randomized, placebo-controlled studies of agents evaluated for Alzheimer's disease (clinical data) and MCI (MRI data)

	Galantamine (2 years)	Donepezil (2 years)	Solanezumab (18 months)
Mortality	↓42 %*	ns	n/a
Cognitive loss	↓48 %*[a]	↓15 %*	↓34 %*
Functional loss	↓25 %*	↓9 %*	ns
Global atrophy	↓34 %* (24 months, MCI)	ns (29 months, MCI)	ns (18 months, AD)
Estimated cost[b]	10 bn	10 bn	100 bn

Data from Hager et al. (2014), Scheltens et al. (2004), Jack et al. (2008), AD 2000 Collaborative Group 2000, Prnewswire.com (2012)

Galantamine is not approved or recommended for patients with MCI

*p values range from .011 to <.0001

[a]Patients on galantamine without memantine

[b]Based on treating the Alzheimer's patients in the USA for 1 year, in billions of US dollars

function, and brain itself to degrees not seen with donepezil, nor with solanezumab. Galantamine should not be used in MCI. However, for patients with AD, or AD with cerebrovascular disease, there is no comparable treatment currently available. Galantamine is a well-known medication which has been used for many years and is relatively inexpensive. It seems that patients with AD or mixed dementia should have the opportunity to be treated with galantamine.

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