

# Update on Alzheimer Drugs (Galantamine)

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**Background:** Deficient cholinergic function contributes to the cognitive and behavioral signs and symptoms of Alzheimer disease (AD). A successful treatment approach in AD has been the enhancement of cholinergic function by cholinesterase inhibitors.

**Review Summary:** Galantamine is a cholinesterase inhibitor and allosteric modulating ligand at nicotinic cholinergic receptors. Galantamine 24 mg/d has been demonstrated consistently effective compared with placebo for the cognitive, functional, and behavioral aspects of Alzheimer's disease in large multicenter trials. Cognition and function on average are preserved for 12 months in Alzheimer disease patients receiving galantamine. It is safe and very well tolerated when dosage is escalated gradually.

**Conclusions:** Galantamine is a valuable addition to agents available for the pharmacologic treatment of AD.

**Key Words:** cholinesterase inhibitor, galantamine, Alzheimer disease

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## PHARMACOLOGY

Galantamine is a tertiary alkaloid originally derived from bulbs of the *Amaryllidaceae* family of flowering plants that include daffodils and the common snowdrop (*Galanthus woronowii*). Galantamine reversibly and specifically binds to the active site of acetylcholinesterase (ACHE), thereby inhibiting the enzyme that hydrolyzes the neurotransmitter acetylcholine into acetate and choline.<sup>1</sup> The resultant increased concentrations of acetylcholine in the synaptic cleft enhance cholinergically mediated neurotransmission. Such enhanced cholinergic neurotransmission offers an approach to ameliorating those cognitive deficits in Alzheimer disease (AD) that result from the repeatedly demonstrated cholinergic deficiency in this disorder.<sup>2,3</sup>

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## *Galantamine reversibly and specifically binds to the active site of acetylcholinesterase.*

ACHE inhibition is a property galantamine shares with the other clinically available drugs demonstrated to enhance cognitive function in AD (e.g., donepezil and rivastigmine). Although the ACHE inhibitor activity of galantamine appears weaker than that of either donepezil or rivastigmine,<sup>4</sup> its therapeutic effects on AD cognitive function are at least comparable to the effects of these other agents (see below). These observations suggest that the therapeutic effects of galantamine in AD are mediated by an additional mechanism. Such a potential other mechanism is allosteric modulation of nicotinic cholinergic receptor (nAChR) activity.<sup>5</sup> An allosteric modulator interacts with a receptor at a binding site distinct from that which recognizes the natural agonist. Galantamine binds to an allosteric site on the nAChR and acts synergistically with acetylcholine to facilitate nAChR activation.<sup>6</sup> Because nAChR (in contrast to muscarinic cholinergic receptors) consistently has been demonstrated to be reduced in AD<sup>7,8</sup> and short-term nicotinic agonist administration improves cognition in AD,<sup>9,10</sup> the allosteric ligand potentiating effect of galantamine at nAChR is potentially therapeutically relevant. Given that an allosteric modulator is much less likely than a direct agonist to down-regulate nAChR, long-lasting therapeutic effects are possible. However, such nicotinic effects have not yet been demonstrated clinically.

Galantamine is rapidly absorbed and reaches peak plasma concentrations within 30 minutes to 2 hours.<sup>11</sup> It has low plasma protein binding, a relatively short half-life, and linear pharmacokinetics over the dose ranges of 8–24 mg/d given twice daily.<sup>12</sup> Galantamine is metabolized in the liver by cytochrome P450 isoenzymes CYP3A4 and CYP206.<sup>13</sup> Drugs that substantially inhibit CYP206 or CYP3A4, such as paroxetine, ketoconazole, and erythromycin, could increase galantamine concentrations. Galantamine metabolites do not contribute significantly to drug action. Although mild hepatic

or renal impairment is unlikely to have an impact on galantamine plasma concentrations or adverse effects, galantamine dose should be reduced in patients with moderate hepatic impairment<sup>14</sup> and is contraindicated in severe renal or hepatic disease.

### Preclinical Studies

Rodent models of the central nervous system (CNS) cholinergic deficiency manifested in AD have been used to explore the potential cognitive enhancing effects of galantamine. Spatial learning deficits in rats administered the cholinergic antagonist scopolamine were reversed by galantamine.<sup>15</sup> Similarly, memory and spatial learning deficits in mice in whom cortical cholinergic activity was reduced by nucleus basalis magnocellularis lesions were reversed by galantamine.<sup>16</sup> A series of recent studies has evaluated the effects of the cholinesterase inhibitors physostigmine, donepezil, and galantamine as well as the nicotinic agonist GTS-21, on an eye-blink conditioning paradigm in rabbits.<sup>17</sup> In this nicotinic cholinergically mediated learning paradigm, which is impaired in normal human aging and even more so in AD, galantamine was the most effective in improving performance among all agents evaluated in aged rabbits.<sup>18</sup> Studies are underway in humans to determine if there are differential effects of galantamine vis-à-vis other cholinergic enhancing drugs on eye-blink conditioning.

### Clinical Studies in Alzheimer Disease

Three large, long-term (5–6 months), placebo-controlled, double-blind multicenter clinical trials of galantamine recently have been published.<sup>19–21</sup> They are remarkable for their consistency of treatment outcome as well as for their unique characteristics. In each study, persons meeting stringent criteria for AD were randomized to galantamine or placebo. Treatment effects on cognition, global change in disease severity, and function in activities of daily living were similarly ascertained in each study. In addition, there are informative differences among these studies in dosage escalation regimen, measurement of effects on behavioral neuropsychiatric signs and symptoms, and baseline dementia severity and apolipoprotein E genotype on cognitive response to treatment.

The first study provides information on both 6-month and long-term (one-year) galantamine effects on cognition and function in AD and raises the possibility that galantamine delays symptomatic disease progression.<sup>19</sup> This 6-month placebo-controlled trial, followed by a 6-month open label extension, was conducted at 33 sites in the United States. There were 636 patients with mild to moderate AD [as described by scores of 11–24 on the Mini Mental Status Examination (MMSE)]<sup>22</sup> who were randomized to placebo or galantamine (mean age at randomization was 75 years). The initial dose was 8 mg/d. Dose was then escalated rapidly (by

8 mg/wk) to maintained doses of 24 mg/d or 32 mg/d. At the end of the 6-month placebo-controlled phase, all subjects still meeting initial eligibility criteria were continued for an additional 6 months on open label galantamine, 24 mg per day. Primary cognitive outcome measure was the Alzheimer Disease Assessment Scale 11-item cognitive subscale (ADAS-Cog/II).<sup>23</sup> This scale measures cognitive domains consistently impaired in AD including memory, language, and praxis and has become the standard cognitive assessment instrument in clinical outcome trials in this disorder. It has a score range of 0–70. To obtain a measure of global clinical change that may be more meaningful than modest changes in cognitive function, the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus)<sup>24</sup> was also a primary outcome measure. The CIBIC-Plus is based on separate interviews with patient and caregiver, with scores compared with baseline ranging from 1 (markedly improved) to 7 (markedly worsened). A secondary outcome measure was the Disability Assessment for Dementia (DAD),<sup>25</sup> which provides a functional assessment by measuring basic and instrumental activities of daily living (ADL), participation in leisure activities, and executive function. DAD scores range from 0 to 100.

To evaluate 6-month efficacy data, an observed case analysis was performed. Galantamine was significantly superior to placebo at 6 months on the ADAS Cog II, with treatment effects of 3.9 points at 24 mg/d and 3.8 points at 32 mg/d. Galantamine also produced a better outcome than placebo on the CIBIC-Plus (both doses  $P < 0.05$ ). Although DAD scores did not differ significantly from placebo at 6 months, at 12 months both mean ADAS Cog II and DAD scores had not significantly changed from baseline in patients receiving galantamine 24 mg/d for the entire 12-month period. In contrast, values for those patients originally randomized to placebo had substantially declined.

Adverse effects were predominantly gastrointestinal. During the placebo-controlled phase of the study, nausea occurred in 37% of galantamine 24 mg/d subjects; 44% of galantamine 32 mg/d subjects; and 13% of placebo subjects. Vomiting occurred in 21% of galantamine 24 mg/d subjects, 26% of galantamine 32 mg/d subjects, and 8% of placebo subjects. These adverse effects mostly were reported during the rapid dose escalation phase and were uncommon during maintenance treatment. Apolipoprotein E genotype did not affect response to galantamine.

Data from this study suggest that galantamine 24 mg/d on average maintains cognition and function in mild to moderate AD for 12 months. In addition, subjects initially randomized to placebo for 6 months and then treated with open label galantamine 24 mg/d for the subsequent 6 months had more impaired cognitive function at 12 months than those subjects receiving galantamine 24 mg/d for the entire 12-month study duration. These 12-month data are consistent with symptomatic slowing

of disease progression at this dose of galantamine. These data also suggest that rapid galantamine dose escalation often induces nausea or vomiting for several days following dose increases. This observation provided rationale for the slow dose escalation study described below.

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A second, similarly designed, large 6-month placebo-controlled multicenter study was performed in Canada and Western Europe.<sup>20</sup> A total of 653 patients with mild to moderate AD were randomized to placebo, galantamine 24 mg per day, or galantamine 32 mg per day. MMSE scores ranged from 11 to 24, and mean age was 72 years. Dose was escalated rapidly (over 3–4 weeks) to maintenance levels. Consistent with the study described above, galantamine was significantly superior to placebo in the observed cases analysis on the ADA-cog<sup>5</sup> measure of cognition (3.1 points for 24 mg/d and 4.1 points for 32 mg/d) and the CIBIC-plus. In this study, function as measured by the DAD deteriorated significantly less in both galantamine groups than in the placebo group. When subjects were divided into mild and moderate severity groups at baseline (MMSE  $\geq$  18 and MMSE < 18, respectively) in an exploratory analysis, the benefit of galantamine was greatest in the moderately severe subjects. Treatment difference between 32 mg/d galantamine and placebo in these more severely impaired subjects was 7 points on the ADAS-cog II and between 24 mg/d and placebo were 5 points on the ADAS-cog II. Predictably, the rapid dose escalation produced a high incidence of gastrointestinal adverse effects. Nausea, usually occurring following dose increases, was reported by 12% of placebo subjects, 37% of galantamine 24 mg/d subjects, and 40% of galantamine 32 mg/d subjects. As in the first study,<sup>19</sup> there was no effect of apolipoprotein genotype on treatment outcome.

A third large multicenter study investigated the efficacy and tolerability of galantamine using a slow dose escalation schedule of up to 8 weeks.<sup>21</sup> In this study, 978 patients with mild to moderate AD were randomized to either placebo or galantamine escalated to final maintenance doses of 8, 16, or 24 mg/d. MMSE scores ranged from 10 to 22, and mean age was 77 years. As in the previously described studies, cognitive function was assessed with the ADAS-cog, and global clinical change with the CIBIC-Plus. Function was assessed with the recently developed AD Cooperative Study Activities of Daily Living

Inventory (ADCS/ADL).<sup>26</sup> A unique feature of this study was a careful assessment of behavioral symptoms of AD using the Neuropsychiatric Inventory (NPI).<sup>27</sup> The NPI assesses frequency and severity of signs and symptoms in 10 behavioral domains commonly affected in AD (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant behavior). NPI scores range from 0 to 120. Another important feature of this study was the slow dose escalation schedule. For example, those randomized to an ultimate maintenance dose of 24 mg/d were started at 8 mg/d for 4 weeks, then increased to 16 mg/d (8 mg bid) for 4 weeks, and finally to 24 mg/d (12 mg bid) for the duration of the study.

Results again indicated efficacy of galantamine for a broad spectrum of AD signs and symptoms including behavior. Galantamine significantly improved cognitive function relative to placebo at 5 months, with treatment effects on the ADAS-cog of 1.7 points at 8 mg/d, 3.3 points at 16 mg/d, and 3.6 points at 24 mg/d. Galantamine also was significantly superior to placebo in the CIBIC plus assessment of change in overall clinical severity. Function at 5 months as measured by the ADCS/ADL decreased significantly less in the galantamine 16 mg/d and 24 mg/d groups than in the placebo group and was maintained at baseline levels in the 16 mg/d group. Galantamine also had a favorable effect on behavioral symptoms as measured by the NPI, with significantly lower (better) scores at 5 months for both 16 mg/d and 24 mg/d than placebo.

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The slow dose escalation regimen produced a much lower incidence of adverse effects than the rapid dose escalation in the studies described above.<sup>19,20</sup> Discontinuations due to adverse effects did not differ significantly among groups (10% in the 24 mg/d group, 7% in the 16 mg/d group, 6% in the 8 mg/d group, and 7% in the placebo group). The majority of adverse events, including gastrointestinal events, were mild. For example, nausea (usually transient) occurred in 5% of placebo patients, 6% of 8 mg/d patients, 13% of 16 mg/d patients, and 17% of 24 mg/d patients. These nausea rates are comparable to those observed in trials of donepezil 10 mg/d.<sup>28</sup>

Taken together, these 3 studies demonstrate consistent positive effects of galantamine on a broad spectrum of AD clinical features. In each study, there was a significant increase at 3 months compared with baseline in cognition

measured by ADAS-cog scores and a treatment difference favoring galantamine 24 mg over placebo by between 3 and 4 points at 5 and 6 months. Galantamine positive effects on global ratings of change in disease severity and assessments of ADLs also were similar among studies. The positive effects of galantamine on behavior in the 5-month study are consistent with results of previous studies of other cholinesterase inhibitors, which are either not available (metrifonate),<sup>29</sup> or of limited utility (tacrine) because of toxicity.<sup>30</sup> The occurrence of unpleasant gastrointestinal adverse effects during rapid dose escalation is substantially reduced by gradual dose escalation at 4-week intervals. In none of these multicenter studies did galantamine effects on sleep differ from placebo.

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### **Galantamine in Disorders Other than AD: Vascular Dementia and Mixed AD/Vascular Dementia**

Although AD continues to be the most common etiology of dementia in late life, recent epidemiologic studies suggest that strategically located brain vascular lesions frequently contribute to dementia in persons with concomitant AD.<sup>31,32</sup> These cases of “mixed” dementia together with a smaller number of cases with vascular dementia wholly attributable to cerebrovascular disease comprise an important subgroup of late-life dementia patients. That a presynaptic cholinergic deficit similar to that in AD has been reported in vascular dementia<sup>33</sup> provides rationale for possible therapeutic efficacy of cholinesterase treatment of vascular dementia and mixed AD/vascular dementia.

Galantamine is the only cholinesterase inhibitor for which results of a randomized placebo-controlled trial in vascular and mixed dementia have been published.<sup>34</sup> In this multicenter European 6-month trial, 537 patients with mild to moderate dementia (MMSE = 10–25; age = 75 years) were randomized to galantamine 24 mg/d or placebo. Subjects met either NINDS-AIREN criteria<sup>35</sup> for probable vascular dementia (42%), NINCDS-ADRDA criteria<sup>36</sup> for possible AD with clinical and neuroradiologic evidence of cerebrovascular disease (i.e., “mixed” dementia) (49%). Eight persons were indeterminate, such that investigators were unable to choose definitely between vascular or mixed dementia.

At 6 months, galantamine was significantly more effective than placebo on cognition as measured by the ADAS-cog ( $P < 0.001$ ). Improvement over baseline in galantamine subjects was 1.7 points ( $P < 0.001$ ), whereas placebo subjects deteriorated by 1.0 points compared with baseline ( $P < 0.05$ ). Improvement on galantamine was very similar in the vascular dementia and mixed dementia groups. Interestingly, those vascular dementia subjects randomized to placebo had not significantly deteriorated from baseline at 6 months; the deterioration in the placebo subjects largely was accounted for by the mixed dementia subjects, where rate of decline was similar to that observed in AD subjects randomized to placebo in the studies described above. This lack of deterioration in the vascular dementia group provides some support for the validity of the diagnostic criteria used for vascular dementia. Positive results favoring galantamine also were observed for global change in disease severity as measured with the CIBIC-Plus, activities of daily living and function as measured with the DAD, and behavioral signs and symptoms as measured by the NPI. This study clearly extends the usefulness of galantamine beyond pure AD and helps resolve reluctance to use cholinesterase inhibitors in the presence of cerebrovascular disease that appears to be clinically meaningful.

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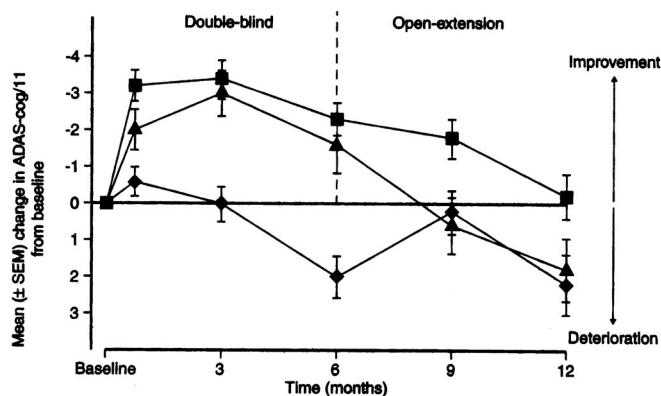
*Galantamine is predicted to reduce overall health care cost savings because medication costs are offset by other health care expenditure reductions.*

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### **Pharmacoeconomics**

Given the high prevalence of AD in later life and the tremendous cost of caring for older persons with AD, it is important to attempt to determine the impact of galantamine treatment in overall health care costs. Ideally, one would randomize persons with AD to galantamine or placebo and follow them prospectively for the duration of their illness to compare both direct and indirect costs of the illness in treated and untreated groups. Such an approach is neither feasible nor ethical for many reasons, among which is the now firmly established efficacy of cholinesterase inhibitors. Given these constraints, modeling techniques based on what is known about the course of untreated AD and utilizing results of available placebo controlled outcome studies can provide estimates of the effects of cholinesterase inhibitors on costs. One such model is the Assessment of Health Economics in Alzheimer Disease (AHEAD),<sup>37</sup> which was developed based on equations relating probability of needing full-time care over time to patient characteristics. Equations were devel-





**FIGURE 1.** Mean change from baseline in 11-item AD Assessment Scale cognitive subscale (ADAS-cog/11) scores over 12 months (observed case analysis). [squl] = Galantamine 24 mg/ galantamine 24 mg; ▲ = galantamine 32 mg/ galantamine 24 mg; ◆ = placebo/galantamine 24mg. (Reprinted with permission from Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology*. 2000;54:2261–2268.)

oped from published data on times until full-time care is needed and until death. The model provides a standard estimation technique that enables comparisons between existing AD management and emerging therapies. The AHEAD model algorithms used to predict time to required full-time care were adapted to Canada to compare AD treatment with galantamine to no specific pharmacologic treatment of AD.<sup>38</sup> Health care costs including drugs were evaluated according to disease stage based on Quebec unit costs and follow-up data from the Canadian Study of Health and Aging.<sup>39</sup> The model predicted that galantamine would reduce duration of full-time care by 10%. For patients with moderately advanced AD, 3.9 patients must be placed on galantamine to avoid 1 year of full-time care. This results in predicted savings of \$2,533 (US) per patient. Thus, galantamine is predicted to reduce overall health care cost savings because medication costs are offset by other health care expenditure reductions.

An intuitively attractive approach to evaluating the effect of AD on indirect costs is time spent by caregivers (“caregiver burden”) on behalf of their family member with AD.<sup>40</sup> A recent analysis has estimated galantamine effects on caregiver burden by comparing galantamine and placebo effects on time spent by caregivers assisting AD patients with activities of daily living.<sup>41</sup> It used data generated by a caregiver time questionnaire administered during the large 6-month European and Canadian multicenter study described above.<sup>20</sup> At 6-month evaluation, caregiver time in the galantamine 24 mg/d group was reduced by 38 minutes compared with an increase of 23 minutes in the placebo group. The reduction in caregiver time observed during double-blind

galantamine treatment was maintained during a subsequent 6-month open-label galantamine treatment period.

## CONCLUSION

Multiple large studies of galantamine have demonstrated that this cholinesterase inhibitor and nicotinic allosteric modulator is effective for a broad spectrum of AD signs and symptoms. Cognition and function on average are maintained at baseline levels for 1 year. Long-term follow-up of AD patients in open label extensions of placebo-controlled trials suggests that cognitive benefits persist for up to 3 years.<sup>42</sup> Galantamine is safe and well tolerated. Gastrointestinal adverse effects are minimized by slow dose escalation at four-week intervals to the maximum recommended dose of 24 mg/d given as 12 mg twice daily. Galantamine has few, if any, adverse effects on sleep. Galantamine also has been demonstrated effective in vascular dementia and in patients whose cerebrovascular pathology interacts with AD to produce “mixed” dementia. Galantamine multicenter studies have been characterized by their consistency in magnitude of positive response compared with placebo.

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