Galantamine: A New AcetylCholinesterase Inhibitor for the Treatment of Alzheimer’s Disease

Martin S. Maltz, RPh, MS and Harold L. Kirschenbaum, MS, PharmD

Alzheimer’s disease (AD), a subtype of dementia, is a devastating neurological disorder characterized by a profound decrease in cognitive function and a progressive loss of memory. As the disease advances, patients gradually lose the ability to perform routine daily tasks and often exhibit behavioral disturbances. Although a definitive diagnosis of AD can only be made with a brain autopsy or biopsy, for practical purposes, a diagnosis is established clinically through cognitive assessment, physical examination, laboratory studies, and neurological imaging.

Pathologically, patients with AD present with β-amyloid deposits, senile plaques, and neurofibrillary tangles in the basal forebrain and cerebral cortex regions of the brain. Accompanying this neuronal degeneration is a significant loss of cholinergic neurons and their target nerve cells, which subsequently leads to a decrease in acetylcholine (ACh) neuronal transmission. This cholinergic deficiency in the brain is hypothesized to be responsible for the decrease in cognitive function and memory loss associated with AD. Although there is a genetic predisposition for developing AD, increasing age is a significant risk factor. In a community population in the U.S., the prevalence of AD was shown to be approximately 10% in individuals over 65 years old, compared with approximately 19% for persons 75 to 84 years of age. At 85 years of age, the prevalence of AD is 14 times higher than in the population of 65- to 70-year-olds. With the rapidly increasing senior population, AD is becoming a very common and costly disease. Worldwide, AD affects 15 million people, and nearly $100 billion is spent annually in indirect and direct costs in the U.S. alone.

The focus of therapy for AD is primarily to manage symptoms, but an attempt is made to increase the concentration of ACh in the degenerating regions of the brain. Over the last decade, acetylcholinesterase inhibitors (AChEIs), agents that inhibit acetylcholinesterase (AChE) activity, have been the mainstays of AD therapy. They work by increasing ACh concentrations, and thus their availability for synaptic transmission. Previously marketed agents in this class, in the U.S. and Europe, include tacrine (Cognex, Parke Davis), donepezil (Aricept, Pfizer), and rivastigmine (Exelon, Novartis).

In clinical trials, most of these products were shown to improve cognitive function modestly and to have acceptable tolerability profiles. The exception is tacrine, which is rarely used because of its potential to induce severe hepatic complications. Unfortunately, the current therapies for AD are only symptomatic and do not halt the progression of the disease. Nonetheless, these agents are the only compounds approved for the treatment of AD; therefore, the development of newer agents that are designed to be more effective and have fewer side effects is a high priority.

FDA APPROVAL

In February 2001, the FDA approved galantamine (Reminyl, Janssen) for the treatment of patients with mild to moderate AD. The purpose of this review is to describe the pharmacology, clinical efficacy, and adverse-effect profile of this new agent. Originating from the daffodil plant, Narcissus pseudonarcissus, galantamine brings new attention to the growing class of AChEIs by touting a proposed dual mechanism of action—although its precise mechanism of action has not been established.

PHARMACOLOGY

Numerous in vivo and in vitro receptor assays have shown that galantamine reduces the cholinergic deficit in the brain through two independent mechanisms of action: a competitive and reversible inhibitor of AChE and modulation of nicotinic receptors. By serving as a nonselective, reversible inhibitor of AChE, a higher concentration of intact ACh for neuronal activity results. At the recommended dosage, galantamine inhibits 25% to 65% of AChE activity. This inhibition is short-lived and reverses within 24 hours of discontinuation of therapy. Galantamine is 53 times more selective for AChE than butyrylcholinesterase (BuChE), an enzyme responsible for metabolizing ACh in the periphery. This could be beneficial, as inhibition of BuChE can cause peripheral ACh-related side effects.

Galantamine also works by modulating nicotinic receptors, causing them to be more sensitive to ACh. This allows for greater ACh neuronal activity where the ACh concentration is low. In vitro studies suggest that nicotinic modulation...
might also facilitate the release of glutamine and serotonin, which are associated with increased learning and mood stabilization, respectively. Furthermore, galantamine has been shown to potentiate the release of GABA, which might aid in quelling the aggression associated with AD. Additional studies are necessary to further elucidate these proposed mechanisms.

**PHARMACOKINETICS**

The pharmacokinetic properties of galantamine were investigated in both healthy volunteers and in patients with AD. Studies show that galantamine is 90% bioavailable following oral administration and the time it takes to reach its maximum concentration (T_{max}) after one hour. Food decreases the maximum concentration (C_{max}) by 25%, and delays T_{max} by one hour but does not alter area under the concentration curve (AUC), which is indicative of total absorption. Following a single 10-mg dose in eight healthy volunteers, galantamine demonstrated first-order pharmacokinetics. In addition, galantamine has a large volume of distribution (Vd) (175L) and is 18% protein-bound.

The metabolism of galantamine is primarily (about 75%) through the hepatic cytochrome P-450 enzyme system; CYP2D6 and CYP3A4 are the principal enzymes involved. Galantamine is also glucuronidated and excreted unchanged in the urine. Following hepatic metabolism, galantamine is transformed into numerous metabolites, including O-demethylgalantamine, N-demethylgalantamine, and epigalantamine. Although some of these metabolites inhibited AChE in vitro, these effects were not shown to be clinically significant in vivo.

**EFFICACY STUDIES**

The efficacy of galantamine was evaluated in several large, multicenter trials in North America and Europe. Most notable are the USA-1, USA-10, and the International-1 Study Group. These studies examined the efficacy and safety of galantamine in patients with AD in both short- and long-term settings. The primary outcome measurements used in these studies included the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog) and the Clinician’s Interview Based Impression of Change Scale (CIBIC-plus). The ADAS-cog is an 11-item standardized assessment of cognitive function that utilizes a scale of 0 to 70. The CIBIC-plus is a seven-point rating scale that assesses patient cognition, behavior, and activities of daily living through interviews with both the caregiver and the patient. Scoring a lower number on these tests indicates increased cognitive function.

**USA-1 Study Group**

The USA-1 Study Group examined the efficacy and safety of galantamine in patients with mild to moderate AD. This study was conducted in two phases. First, two doses of galantamine were compared to placebo in a double-blind fashion for six months. Then, the long-term effects of galantamine were assessed in an open-label extension study for an additional six months. The inclusion criteria included a history of a progressive decline in cognitive function over the previous six-month period, a diagnosis of AD, mild to moderate dementia, and a score of 12 or greater on the ADAS-cog. Patients were excluded if they exhibited any other neurodegenerative disease or physiological complications that would prevent completion of the trial. In addition, patients treated with an AChE inhibitor during the three months prior to the study were excluded.

Initially, 764 patients were screened in a single blind, four-week preliminary trial. Following this run-in period, 636 patients were randomized to receive a twice-daily dose of a placebo (n=123) or galantamine. The patients randomized to the active treatment received galantamine 8 mg/day in week one, 16 mg/day in week two, and 24 mg/day in week three. During the fourth week, one group of patients (n=212) continued to receive 24 mg/day, while the other group (n=211) received 32 mg/day. This phase of the trial continued for an additional five months.

After this six-month phase, patients entered an open-labeled extension study in which all participants received galantamine 24 mg/day for 5.5 months. The primary outcome measurements were the ADAS-cog/11 and the CIBIC-plus. In the initial phase, measurements were performed at baseline, three weeks, three months, and six months. In the extension phase, assessments were made at three and six months. A total of 268 patients completed the study.

The researchers reported a significant improvement from baseline at six months for those receiving galantamine 24 mg/day (-1.7 points, P<0.001) and 32 mg/day (-1.6 points, P=0.02). Patients who received placebo showed a significant decline in ADAS-cog/11 score compared to baseline (+2.2 points, P<0.001). Also, compared with the group that received placebo, at six months, there was a significant difference in the change in the ADAS-cog/11 score from baseline for the groups that received galantamine 24 mg/day (-3.9 points, P<0.001) and galantamine 32 mg/day (-3.8 points, P<0.001). At 12 months, the group that received galantamine 24 mg/day maintained cognitive function relative to baseline. However, patients who received galantamine throughout the entire study demonstrated a significantly (P<0.03) better outcome compared with the group of patients who received placebo for the initial six months.

Moreover, at three and six months, there was a significant improvement in the CIBIC-plus scores for both galantamine 24 mg/day (P<0.05) and 32 mg/day (P<0.05) groups compared with the placebo group. After six months, 70% of patients who received galantamine 24 mg/day and 68% of those who received 32 mg/day showed improvement or remained stable, compared with 55% of patients who received placebo. After 12 months, mean assessment scores were not significantly different from baseline scores. Hepatotoxicity was not noted.

**USA-10 Study Group**

The focus of this study was to address the efficacy and tolerability of galantamine in patients with mild to moderate AD. Originally 1,178 patients were
screened for inclusion; 978 were randomized to receive one of four treatment protocols. Patients received either a placebo for five months; galantamine 8 mg/day for five months; galantamine 8 mg/day for four weeks, which was then increased to 16 mg/day for 17 weeks; or galantamine 8 mg/day for four weeks, followed by galantamine 16 mg/day for four weeks, which was then increased to 24 mg/day for 12 weeks.

For study inclusion, patients needed to demonstrate a progressive decline in cognitive function over a six-month period, a score of 10 on a Mini Mental State Exam, and a score of greater than 18 on the ADAS-cog. Patients were excluded if they exhibited significant cardiovascular disease, other degenerative neurological conditions, or hepatic, renal, and endocrine disorders.

All patients received the ADAS-cog and CIBIC-plus tests at baseline and repeated the examinations after five months. At the conclusion of the study, the group of patients who were treated with galantamine 16 mg/day and 24 mg/day showed a significant improvement in ADAS-cog test results (-1.4 points, \( P<0.001 \); -1.4 points, \( P<0.001 \), respectively) compared with placebo. This improvement was not noted for the galantamine 8 mg/day treatment group.

In addition, a significantly greater improvement in the ADAS-cog score from baseline was noted in the groups of patients that received 16 mg/day (-1.5 points, \( P<0.001 \)) and 24 mg/day (-1.8 points, \( P<0.01 \)) compared with the placebo group (+1.8 points, \( P<0.001 \)). Furthermore, data from the CIBIC-plus revealed that groups treated with galantamine 16 and 24 mg/day showed an overall significant improvement in clinical status compared to patients in the placebo group (\( P<0.001 \)) and 8 mg/day (\( P<0.05 \)) groups. In general, galantamine was well-tolerated.

**International-1 Study Group**

This six-month, parallel group, placebo-controlled study evaluated the efficacy and safety of galantamine in patients with mild to moderate AD. In Europe and Canada, 653 patients from 86 centers were randomized to receive a twice-daily dose of either galantamine or placebo. Galantamine was administered as a regimen of 8 mg/day for week one, then increased to 16 mg/day for week two, and then 24 mg/day for week three. During week four, patients were randomized to continue to receive galantamine 24 mg/day or were increased to 32 mg/day for the remainder of the study. Primary outcome measurements included the ADAS-cog/11 and the CIBIC-plus. Patients in the two galantamine groups demonstrated better cognitive function than the patients in the placebo group. This improvement was noted in the significantly greater mean change in the ADAS-cog/11 scores at three and six months for the 24 mg/day group (-2.9 points, \( P<0.001 \)) and 32 mg/day group (-3.1 points, \( P<0.001 \)) compared to the placebo group. At six months, both treatment groups also showed significantly better CIBIC-plus scores than those who received placebo. Galantamine was shown to be effective and was well-tolerated.

**ADVERSE EFFECTS**

The adverse effects associated with galantamine appeared to be mild to moderate in severity, and were mostly limited to the gastrointestinal tract. In studies assessing the safety of galantamine, the most common adverse effects, which occurred in approximately 5% more patients in the galantamine group than in the placebo group, were diarrhea, nausea, vomiting, anorexia, weight loss, headache, and dizziness. Other adverse effects that occurred in at least 1% of patients included chest pain, flatulence, and incontinence.

Infrequent adverse effects occurring in at least 0.1% to 1% of patients included hypotension, cardiac failure, vertigo, gastrointestinal, increased saliva, AV block, palpitations, QT prolongation, hyperglycemia, and increased micturition frequency.

In the International-1 Study Group, 18% of patients in the galantamine group discontinued the study prematurely because of side effects, compared to 9% of patients who took placebo. The most common cause for this discontinuation was nausea. At least 50% of patients who withdrew from the study did so in the dose-escalation phase of the study. This pattern of discontinuation was also observed in the USA-1 Study and USA-10 Study Groups, where patients discontinued therapy primarily during the dose-escalation periods. It appears that slow dose escalation might enhance the tolerability of galantamine. These study groups also reported incidences of slight weight loss in the galantamine group that appeared to be dose-related. The most common adverse events noted in the prescribing information are nausea, vomiting, diarrhea, anorexia, and dizziness.

**DRUG INTERACTIONS**

Galantamine is metabolized by the hepatic enzymes CYP2D6 and CYP3A4. Based on pharmacokinetic studies, potent inhibitors of these enzymes can increase the AUC of galantamine. For example, agents such as ketoconazole and paroxetine have been shown to increase the AUC of galantamine by 30% to 40%, whereas erythromycin and cimetidine raised the AUC by more than 10%. In addition, co-administering galantamine with fluoxetine and quinidine resulted in more than a 25% decrease in hepatic clearance.

Although the elimination of galantamine is delayed as a result of these interactions, there are no data to support any clinical significance. Nonetheless, caution should be exercised before initiating or stopping a concomitant agent that affects or is affected by the CYP2D6 or CYP3A4 enzymes. Furthermore, in vitro studies determined that galantamine does not inhibit CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2D6 or CYP2E1 enzymes. Because of its pharmacological properties, galantamine can interfere with anticholinergic agents and have a synergistic effect with other AChEIs, neuromuscular blocking agents, and cholinergic agonists. Concomitant use of these agents with galantamine should be avoided.

**PHARMACOECONOMICS**

Cost-effectiveness data for galantamine are limited; however, studies with tacrine showed beneficial economic outcomes. Considering that galantamine is a potential safer and more effective agent than tacrine, one might assume that it is equally,
if not more, cost-effective. In an economic model relating improved cognitive function to increased economic savings, patients living at home showed increased cost savings while on a newer AChEI. This outcome, however, was not realized for patients in an institutional setting, possibly because of the increased costs incurred with providing treatment.26 There are no economic data comparing the cost-effectiveness of one new AChEI against another; however, one must consider that whereas other AChEIs are given as single daily doses, galantamine is dosed twice daily. It also requires patients to undergo repeated assessments to tailor an effective dose. When taken twice daily, the average wholesale price (AWP) for a one-month supply of all strengths of galantamine is $129.60.27

DOSSAGE
Galantamine should be initiated at 4 mg twice daily for a minimum of four weeks. If it is well-tolerated, the dose may be increased to 8 mg twice daily, with a minimum delay of four weeks before increasing to 12 mg twice daily if needed. Studies do not show any significant difference in effectiveness between 16 and 24 mg/day.11 Patients with moderately impaired liver function (Child-Pugh score of 7-9) or with moderate renal impairment should not exceed 16 mg/day. Galantamine is not recommended in patients with severe hepatic impairment (Child-Pugh score of 10-15) or severe renal impairment (creatinine clearance <9 ml/min).11

PATIENT INFORMATION
Galantamine is available as 4-, 8-, and 12-mg tablets. Patients should be advised to take galantamine with food and not to skip any doses, because the beneficial effects of galantamine are lost after the patient discontinues therapy. When titrating to a higher dose, it is important to increase the dose slowly, because of the risk of gastrointestinal effects, such as nausea. If there is an interruption in therapy for more than a few days, patients should be restarted on a lower dose. Finally, patients with a history of asthma, seizures, stomach ulcers, and cardiovascular and genitourinary conditions should be monitored for possible exacerbation of these conditions.11

CONCLUSION
In summary, galantamine is a new AChEI with a dual mechanism of action. Whether this mechanism provides added clinical benefit remains to be proven. In human efficacy studies, galantamine was shown to be significantly more effective than placebo in treating the symptoms of patients with mild to moderate AD, and is generally well-tolerated. Additional considerations for formulary addition, however, should be galantamine’s twice-daily dosing, the need to titrate to an effective dose, and the relatively high incidence of nausea. Galantamine appears to be a good choice for selective patients with mild to moderate AD. ■

REFERENCES