

# Current Treatments for Alzheimer's Disease: Cholinesterase Inhibitors

Rachelle S. Doody, M.D., Ph.D.

The current recommended standard of care for the symptomatic treatment of mild to moderate Alzheimer's disease is cholinesterase inhibitors. In short- and long-term studies, the 3 cholinesterase inhibitors most commonly used, donepezil, rivastigmine, and galantamine, have demonstrated efficacy in improving not only cognition but also function and behavior in patients suffering from mild to severe cases of Alzheimer's disease and other forms of dementia. However, the benefits of cholinesterase inhibitors in treating the broad spectrum of symptoms associated with Alzheimer's disease are not sustained indefinitely, and the illness continues to progress even while patients are receiving treatment. Additionally, while temporary stabilization may occur, there is typically only a modest improvement from baseline, and side effects from treatment with cholinesterase inhibitors can be too severe for some patients to tolerate. Therefore, additional therapies for Alzheimer's disease still need to be developed that include more tolerable agents with alternative mechanisms of action and broader efficacy.

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**A**cetylcholinesterase is a key inactivator of neuro-ally released acetylcholine. It is commonly understood that the inhibition of the enzyme acetylcholinesterase can boost the action of acetylcholine long enough to enhance cognition in patients suffering from Alzheimer's disease.<sup>1,2</sup> Recently, the American Academy of Neurology issued an evidence-based practice parameter<sup>3</sup> stating that the current standard of care for the symptomatic treatment of mild to moderate Alzheimer's disease is cholinesterase inhibitors. Additionally, numerous short- and long-term placebo-controlled studies have demonstrated the efficacy of cholinesterase inhibitors in improving not only cognition<sup>4-7</sup> but also function<sup>4,7-9</sup> and behavior<sup>7,10</sup> in patients suffering from mild to severe cases of Alzheimer's disease as well as other forms of dementia.<sup>11</sup>

Donepezil, rivastigmine, and galantamine are 3 cholinesterase inhibitors that are frequently used to treat Alzheimer's disease. Each of these agents enhances declining cholinergic function, a key characteristic of Alzheimer's disease. Donepezil inhibits acetylcholin-

esterase<sup>1</sup>; rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase; and galantamine inhibits acetylcholinesterase while allosterically modulating nicotinic cholinergic receptors.<sup>1</sup> This review will present data on each agent from short-term, placebo-controlled trials; long-term, placebo-controlled trials up to 1 year in duration; and open-label trials occurring after double-blind, placebo-controlled trials that lasted up to almost 3 years. Together, these studies demonstrate the benefit of cholinesterase inhibition in improving cognition, function, and behavior in patients suffering from mild to severe Alzheimer's disease.

## EFFECTS ON COGNITIVE SYMPTOMS

Short-term (typically 3- to 6-month), randomized, double-blind, placebo-controlled trials have been conducted to examine the effects of cholinesterase inhibition on the cognitive symptoms of mild to moderate Alzheimer's disease as defined by a score of  $\geq 10$  on the Mini-Mental State Examination (MMSE). Instruments that were employed to monitor cognitive functioning included the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog), considered the gold standard for assessing cognition in clinical trials of antidementia drugs, and the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus), which allows physicians to assess the patient's global status by asking questions of the patient and caregiver to determine what changes have occurred in the patient's cognition, functioning, and behavior. This assessment essentially creates a gestalt of patient improvement or nonimprovement for the physician.

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*From the Department of Neurology, Baylor College of Medicine, Houston, Tex.*

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*Corresponding author and reprints: Rachelle S. Doody, M.D., Ph.D., Baylor College of Medicine, 6550 Fannin, Suite 1801, Houston, TX 77030 (e-mail: rdoody@bcm.tmc.edu).*

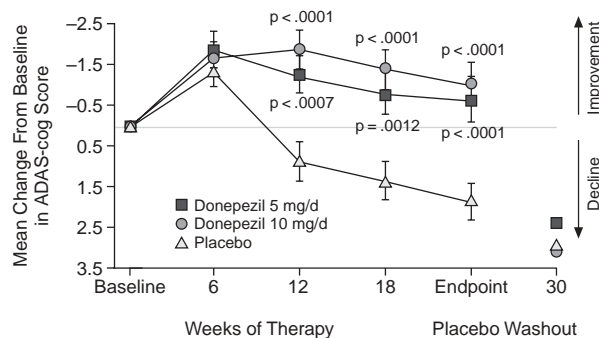
### Donepezil

Rogers et al.<sup>6</sup> investigated the efficacy and safety of donepezil in treating patients with mild to moderate Alzheimer's disease. Patients were randomly assigned to 1 of 3 groups to receive either 5 mg/day of donepezil (N = 154), 10 mg/day of donepezil (N = 157), or placebo (N = 162) and were assessed in 6-week intervals for 24 weeks, followed by a 6-week, single-blind placebo washout. Efficacy was determined using the ADAS-cog, the CIBIC-plus, the MMSE, the Clinical Dementia Rating-Sum of the Boxes (CDR-SB), and the patient-rated Quality of Life (QoL) scales. At weeks 12, 18, and 24, ADAS-cog scores were improved considerably in the donepezil groups relative to placebo. Significant improvements ( $p \leq .005$ ) in global functioning were additionally observed at endpoint in both drug groups on the CIBIC-plus, MMSE, and CDR-SB. No apparent benefit was detected on the patient-rated QoL measures, however. After the 6-week washout period, ADAS-cog scores were not significantly different between the 3 groups, indicating that some benefits of the drug may diminish after drug treatment is discontinued. Some benefits, however, did not disappear, suggesting that the comprehensive consequences of washout are still unclear. Side effects primarily were reported most often in the 10-mg/day group and consisted of diarrhea or nausea, but were generally transient and mild. The data indicate that donepezil is a well-tolerated drug that improves cognition in patients with mild to moderate Alzheimer's disease, although the effects of donepezil may diminish after treatment is discontinued. Overall, approximately 80% of patients receiving donepezil stabilized or improved over the 6 months (Figure 1). A 6-month study does not define the duration of benefits over the remaining lifespan, which can be many years for the patient with Alzheimer's disease.

### Rivastigmine

In a 6-month randomized trial of rivastigmine, Corey-Bloom et al.<sup>4</sup> measured the efficacy and safety of rivastigmine for patients with mild to moderate Alzheimer's disease, determining the change from baseline in the ADAS-cog score for a placebo group and 2 active drug treatment groups. Patients were randomly assigned to receive either 1 to 4 mg/day of rivastigmine (N = 191), 6 to 12 mg/day of rivastigmine (N = 143), or placebo (N = 185) for 26 weeks. Results indicated that in ADAS-cog scores, the group that received 6 to 12 mg/day of rivastigmine increased almost 1 point above baseline, compared with an approximate 4-point decline in scores for the placebo group and a 2-point decline for the 1- to 4-mg/day group by the end of the 26-week trial. The 6- to 12-mg/day dose of rivastigmine was the most consistently effective in patients with mild to moderate Alzheimer's disease. Rivastigmine was not associated with any increase for mortality or significant adverse effects, but

Figure 1. Response to Donepezil Treatment in a 6-Month Study<sup>a</sup>



<sup>a</sup>Reprinted with permission from Rogers et al.<sup>6</sup>  
Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale.

was associated with gastrointestinal symptoms and weight loss.

### Galantamine

To assess the effect of galantamine on the cognitive symptoms of Alzheimer's disease, Raskind et al.<sup>5</sup> conducted a 6-month, multicenter, double-blind trial of 636 patients with mild to moderate Alzheimer's disease who were randomly assigned to receive either placebo or 24 or 32 mg/day of galantamine. With no washout following the first 6-month phase, eligible patients entered a second 6-month, open-label trial of the 24-mg/day galantamine dose. Efficacy was determined using the 11-item ADAS-cog (ADAS-cog/11) subscale and the CIBIC-plus as primary measures, while the Disability Assessment for Dementia (DAD) scale was used as a secondary efficacy variable. According to ADAS-cog/11 scale scores at the 6-month point, cognitive functioning for both active drug groups was significantly improved compared with the placebo group: increases of 3.9 points for the 24-mg/day group ( $p < .001$ ) and 3.8 points for the 32-mg/day group ( $p < .001$ ) compared with a decline of almost 2 points for the placebo group.

At the 12-month point, mean ADAS-cog/11 scores were not significantly different from baseline for the 24-mg/day group, indicating that the patients were still stable on cognitive function. When the placebo group crossed over to 24 mg/day of galantamine at 6 months, patients demonstrated a boost over the new baseline but did not catch up with the scores of the original 24-mg/day group. This is an interesting phenomenon that appears to occur with other drugs, as well, and suggests that there is a penalty for a delayed start of drug therapy. Overall, the 24-mg/day group demonstrated the most consistent improvement in cognitive functioning based on ADAS-cog/11 scale scores. Side effects were primarily gastrointestinal symptoms and weight loss and tended to decrease in frequency during long-term treatment.

## EFFECTS ON FUNCTIONAL SYMPTOMS

Functional decline is quite common in Alzheimer's disease; in fact, as the disease progresses, it becomes practically inevitable. In Alzheimer's disease, functional decline is characterized by the loss of ability to perform activities of daily living that range from basic actions such as eating and bathing to more complex endeavors such as shopping and using the telephone. Functional pathology increases caregiver burden and is highly correlated with the decision to place patients in alternative care settings such as nursing homes. A number of studies have been conducted to determine whether the cognitive benefits of cholinesterase inhibitor treatment translate into functional benefits. Functional outcomes are primarily measured using the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), the Progressive Deterioration Scale (PDS), and the DAD scale.

### Donepezil

Mohs et al.<sup>8</sup> examined the effects of donepezil on the preservation of function by conducting a 54-week, double-blind, placebo-controlled, survival-to-endpoint study. The study used a projection of the "time to clinically evident decline in function" as the primary outcome measure. Rather than using a traditional parallel study group that would require patients to remain in a placebo group for 1 year, patients were monitored every 6 weeks for any sign of function loss, and the data were presented as a survival analysis. This research design was chosen primarily to provide a protocol-specified opportunity for patients experiencing even very mild clinical decline to leave the protocol and begin open-label treatment. At entry, patients were required to have a diagnosis of probable Alzheimer's disease, an MMSE score of 12 to 20, a CDR-SB of 1 or 2, a modified Hachinski ischemia score of  $\leq 4$ , and the ability to perform 8 of 10 instrumental tasks of daily living and 5 of 6 basic activities of daily living. Eligible participants (N = 431) were randomly assigned to receive placebo (N = 217) or donepezil at 5 mg/day for 28 days and 10 mg/day thereafter (N = 214). The ADFACS, the MMSE, and the CDR-SB scale were all utilized as outcome measures.

In the first 12 weeks of therapy, there was little differentiation in the reduction of risk of functional decline between the donepezil group and placebo group, as few patients declined in either group. However, from week 12 forward, the probability of clinical worsening in functional ability was greater for the group taking placebo. By endpoint, the median time to clinically evident functional decline had been extended by 5 months for the donepezil group versus placebo; the donepezil group achieved a 38% reduction in the risk of functional decline compared with placebo. Overall, survival curves for the 2 treatment groups were significantly different ( $p = .0019$ ). Donepezil was well tolerated throughout the study with

few adverse events. This study indicates that the cognitive benefits of cholinesterase treatment do translate into the stabilization of daily activities and a reduction in functional decline.

Another study<sup>7</sup> used the DAD scale to assess the efficacy of donepezil in improving functioning in patients suffering from moderate to severe Alzheimer's disease, defined by an MMSE score of 5 to 17 and a Functional Assessment Staging score of  $\leq 6$  at baseline. The 24-week, double-blind, placebo-controlled study included 290 patients randomly selected to receive either 5 mg/day of donepezil for the first 28 days and 10 mg/day of donepezil thereafter (N = 144) or placebo (N = 146). Researchers reported stabilization in function with donepezil treatment according to DAD baseline scores, whereas patients receiving placebo declined substantially.

### Rivastigmine

In the 6-month randomized trial of rivastigmine cited previously, Corey-Bloom et al.<sup>4</sup> also studied the functional benefits of rivastigmine for patients suffering from mildly to moderately severe Alzheimer's disease by determining the mean change from baseline in PDS scores for the placebo group and 2 active drug treatment groups. Researchers concluded that the higher dose group (6–12 mg/day rivastigmine) experienced little decline from baseline (less than 1 point) over the course of the trial, whereas the lower dose group (1–4 mg/day rivastigmine) and the placebo-treated group each declined almost 5 points on the PDS over the 26 weeks. Rivastigmine appeared to be most efficacious at a 6- to 12-mg/day dose for maintaining both functional and cognitive ability in patients with mild to moderate Alzheimer's disease.

### Galantamine

The efficacy of galantamine in maintaining not only cognitive but also functional ability was examined in the trial by Raskind et al.,<sup>5</sup> cited previously. In the first phase, patients were randomly assigned to receive either 24 or 32 mg/day of galantamine or placebo for 6 months. Then eligible patients entered a subsequent 6-month, open-label extension trial of 24 mg/day of galantamine. The DAD scale was used as a secondary efficacy variable to determine whether the cognitive benefits of cholinesterase inhibitor treatment translated into a functional benefit. Researchers found that DAD scores did not significantly worsen from baseline for patients who had received 24 mg/day at the beginning of the 12 months and maintained this treatment dose to endpoint. In contrast, patients who crossed over to 24 mg/day from 32 mg/day or placebo declined almost 5 points in DAD scores after the first 6 months. Study results confirmed that galantamine was effective in maintaining not only cognition but also functioning at 6 months, and this benefit continued to endpoint for patients who had received 24 mg/day for 12 months.

Winblad<sup>9</sup> conducted a separate study that estimated the potential decrease in scores if those patients who were given placebo in the first 6-month trial had continued taking placebo until endpoint. Due to the ethical problems often involved in long-term placebo-controlled studies, historical placebo data are sometimes used to perform long-term drug-placebo comparisons. Winblad used historical 12-month placebo data from a previous study<sup>12</sup> that estimated the annual decrease in DAD scores in untreated patients to be 11 to 13 points. On the basis of this estimate, Winblad determined that patients who had been given placebo for the first 6 months would have declined approximately 13 points from baseline in DAD scores had they continued taking placebo for 12 months. His findings indicated that patients receiving galantamine treatment maintain functional ability considerably longer than do patients not receiving galantamine treatment.

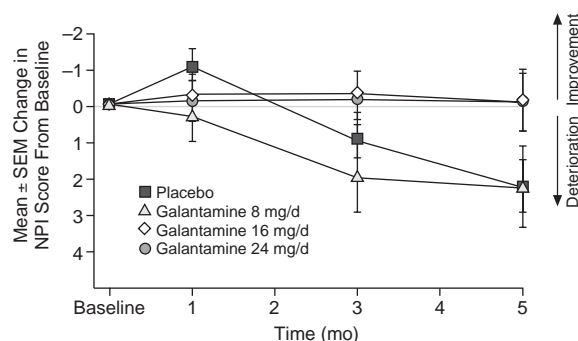
### EFFECTS ON BEHAVIORAL SYMPTOMS

Patients with Alzheimer's disease frequently experience not only cognitive and functional decline but also behavioral disturbances. Estimates of the prevalence of behavioral symptoms vary across studies, depending on how these symptoms are defined and whether the study is cross-sectional or longitudinal. However, these estimates average a prevalence of approximately 60% across studies, and lifetime prevalence rates may be as high as 100% when apathy is included as a behavioral disturbance. Behavioral symptoms are distressing to the patient and upsetting to the caregiver. These psychopathologies frequently include apathy, disturbed mood, disturbed ideation, hallucinations, delusions, altered perceptions, agitation, aggression, anxiety, and sleep disturbances and other circadian reversals. Most studies that assess behavior utilize the Neuropsychiatric Inventory (NPI) as an outcome measure.

#### Donepezil

Feldman et al.<sup>7</sup> investigated the effects of donepezil on the behavioral symptoms of patients suffering from moderate to severe Alzheimer's disease, defined by an MMSE score of 5 to 17 and a Functional Assessment Staging score of  $\leq 6$  at baseline. The 24-week, double-blind, placebo-controlled study included 290 patients who were randomly selected to receive either 5 mg/day of donepezil for the first 28 days and 10 mg/day of donepezil thereafter (N = 144) or placebo (N = 146). Researchers graphed NPI scale scores over a period of 6 months, evaluating behavioral and neuropsychiatric symptoms that included hallucinations, irritability, aberrant motor behavior, delusions, anxiety, depression, elation, disinhibition, nighttime behavior, and eating disorders. Study results indicated that the group receiving 10 mg/day of donepezil improved from baseline by 4.6 points (p = .0001) on the NPI total score at week 24, last observation carried forward

Figure 2. NPI Scores for Patients Treated With 8, 16, and 24 mg/day of Galantamine or Placebo<sup>a</sup>



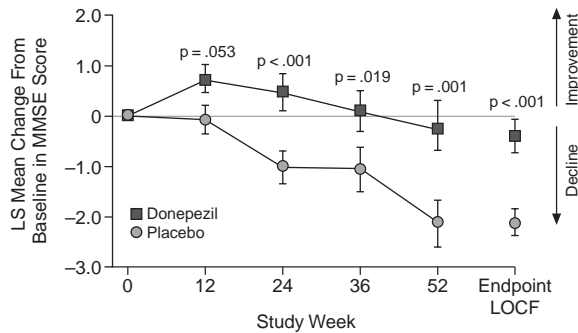
<sup>a</sup>Reprinted with permission from Tariot et al.<sup>10</sup>  
Abbreviation: NPI = Neuropsychiatric Inventory.

(LOCF). Scores for patients who received placebo increased only slightly and then decreased by 1 point at week 24 LOCF. Of the adverse events that were experienced during the trial, the majority were rated mild in severity. Overall, the donepezil-treated group showed significant improvement in NPI scores, and all sub-item variables on the NPI favored donepezil, which had considerable benefits on depression, apathy, and anxiety compared with placebo.

#### Galantamine

Tariot et al.<sup>10</sup> conducted a 5-month, multicenter, placebo-controlled, double-blind study to evaluate the efficacy and tolerability of galantamine in patients with mild to moderate Alzheimer's disease. Although the study did not specifically recruit behaviorally disturbed patients, all of the 978 participants had demonstrated some degree of behavioral abnormality as assessed by the NPI. After a 4-week, single-blind placebo run-in period, participants were randomly assigned to receive placebo or galantamine, which was increased to final maintenance doses of 8, 16, or 24 mg/day. Outcome measures included the NPI to specifically evaluate behavioral and neuropsychiatric symptoms. Results revealed that patients who were given 1 of the 2 currently recommended doses of either 16 or 24 mg/day of galantamine showed little divergence from NPI baseline scores over the course of the 5-month study in behavioral pathology, although they did exhibit a significantly (p < .001) better outcome than those in the placebo group (Figure 2). The behavioral pathology of patients receiving placebo and 8 mg/day of galantamine worsened considerably over the course of the study, with both groups exhibiting a decline in scores of almost 3 points below baseline. Adverse events included gastrointestinal symptoms but overall most adverse events were mild. Galantamine appeared to effectively maintain behavior for

Figure 3. MMSE Scores in a 1-Year, Randomized, Double-Blind, Placebo-Controlled Trial of Donepezil Versus Placebo<sup>a</sup>



<sup>a</sup>Reprinted with permission from Winblad et al.<sup>13</sup>

Abbreviations: LOCF = last observation carried forward, LS = least squares, MMSE = Mini-Mental State Examination.

5 months in patients receiving the recommended doses of either 16 or 24 mg/day.

### LONG-TERM EFFECTS ON COGNITIVE SYMPTOMS

Evidence has suggested that the early cessation of cholinesterase inhibitor treatment in patients with Alzheimer's disease may precipitate a loss of benefits.<sup>6</sup> Recently, some long-term trials have been conducted that examine the benefits of continued cholinesterase inhibitor treatment over time.

#### Donepezil

Winblad et al.<sup>13</sup> conducted a year-long double-blind, placebo-controlled trial to examine the long-term clinical efficacy and safety of donepezil, in which 286 patients with possible or probable Alzheimer's disease were randomly selected to receive either 5 mg/day of donepezil for 28 days followed by 10 mg/day, or placebo. To determine changes in cognition and activities of daily living, patients were assessed using the MMSE at weeks 24, 36, and 52. Patients receiving 10 mg/day of donepezil improved almost 1 point ( $p = .053$ ) from baseline MMSE scores at 36 weeks before dropping slightly below baseline by week 52 ( $p < .02$ ). By the end of the study year, placebo group scores had declined more than 2 points below baseline (Figure 3). The active drug group revealed a tendency for stabilization that was consistent across outcome measures.

A 15-week, double-blind, placebo-controlled study<sup>14</sup> and a 24-week, double-blind, placebo-controlled study<sup>6</sup> that measured the effects of donepezil on the cognitive symptoms of Alzheimer's disease were both used in a multicenter, open-label, 144-week extension crossover study<sup>15</sup> to measure the long-term effects of donepezil on the cognitive symptoms of Alzheimer's disease. In the

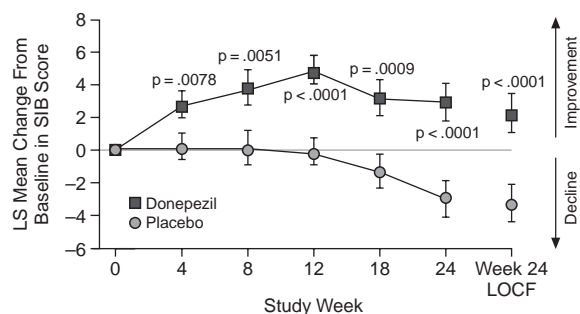
15-week study<sup>14</sup> the mean change from baseline in ADAS-cog scores for patients who received 10 mg/day of donepezil improved almost 4 points, and scores for patients who received 5 mg/day of donepezil improved more than 2 points. Scores for the group assigned to placebo, however, stayed close to the baseline. A 3-week washout period began at the end of the 12 weeks, during which the difference between the donepezil treatment group and the placebo group did not disappear. Following the washout period of 3 weeks, the open-label study began in which all patients took donepezil (initially 5 mg/day for 6 weeks, then 10 mg/day). In the open-label portion, ADAS-cog scores increased to almost 1 point above baseline for patients who had first received placebo and were then crossed over to donepezil. The placebo group did not, however, attain scores as high as those of the original donepezil treatment group. These findings suggest that continued donepezil therapy, even with a brief washout, will result in continued benefits. Additionally, these findings suggest that there may be a penalty for a delayed start of treatment. Researchers of this study concluded that donepezil is an effective and safe drug for the long-term treatment of mild to moderate Alzheimer's disease.

To assess the long-term effects after the 6-week washout with donepezil, patients in the 24-week, double-blind, placebo-controlled study, followed by a 6-week washout, were also enrolled in the same open-label study. After the 6-week washout period, all the ADAS-cog benefits were lost. At the beginning of the open-label extension trial,<sup>15</sup> all patients received 5 mg/day of donepezil for the first 6 weeks. For 90% of these patients, this dose was increased to 10 mg/day of donepezil, while the others remained at the 5-mg/day dose until week 174, depending on the decision of the clinician and the tolerability of the patient. The mean change in ADAS-cog scores from baseline did not improve to the original baseline values of the double-blind trial at any time throughout the extension study; however, each group did gain a slight boost over their new baseline. Side effects throughout the study were transient and generally mild in severity. These findings suggest that interrupting donepezil treatment for as long as 6 weeks might result in patients failing to return to the cognitive and functional levels that they had attained prior to interruption, taking into account the deterioration experienced over time.

#### Rivastigmine

In a 26-week open-label extension of the 26-week, double-blind, placebo-controlled Corey-Bloom et al. study,<sup>4</sup> Farlow et al.<sup>16</sup> examined the long-term efficacy of rivastigmine on the cognitive symptoms of patients suffering from mild to moderately severe Alzheimer's disease. In the previously described Corey-Bloom study, patients were randomly assigned to receive either 1 to 4 mg/day of rivastigmine ( $N = 191$ ), 6 to 12 mg/day of rivastigmine ( $N = 143$ ), or placebo ( $N = 185$ ) for 26 weeks. The group

**Figure 4. SIB Change From Baseline in Depressed Versus Placebo-Treated Patients With Moderate to Severe Alzheimer's Disease<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Feldman et al.<sup>7</sup>  
 Abbreviations: LOCF = last observation carried forward, LS = least squares, SIB = Severe Impairment Battery.

that received 6 to 12 mg/day of rivastigmine increased their ADAS-cog scores slightly above baseline in the early stages of the study, compared with the 1 to 4 mg/day of rivastigmine group and compared with the placebo group, both of which dropped below baseline. Placebo group scores had declined considerably by the end of 26 weeks. In the 26-week extension trial, patients who continued (N = 513) received open-label treatment with 3 mg/day of rivastigmine for the first week, which was increased to 6, 9, or 12 mg/day until endpoint on the basis of tolerability. Additionally, 19 patients were included from the dropout population of the initial trial. By week 52, neither the group that started the double-blind study on placebo nor the group that started at 1 to 4 mg/day improved in cognitive functioning to the extent of the initial 6 to 12 mg/day of rivastigmine group during open-label treatment. Results of this analysis suggested that patients treated with high-dose rivastigmine had greater benefit over the 52-week treatment period compared to the other groups.

**Galantamine**

A recent analysis<sup>17</sup> was conducted to determine the long-term effects of galantamine at 2 years on the cognitive symptoms of Alzheimer's disease. Patients who in previous studies were randomly assigned to receive either 24 or 32 mg/day of galantamine were eventually crossed over to an open-label trial and titrated to a dose of 12 mg b.i.d. trial for 2 years. These patients (N = 212) were then compared with a placebo group (N = 213) from a separate 1-year study, and based on these data, 2 mathematical projections were determined to estimate how the untreated group would have continued to decline. Results indicated that ADAS-cog scores for those who received the active drug for 2 years were approximately 4 points below their original baseline after 2 years of treatment, whereas scores for those who had received placebo would have declined substantially—between 12 and 14 points.

Adverse events were infrequent and rated as mild to moderate: nausea (10.6%), vomiting (4.8%), anorexia (5.5%), weight loss (4.5%). These findings suggest that long-term cognitive worsening is delayed by continued therapy.

**EFFECTS IN MODERATE TO SEVERE ALZHEIMER'S DISEASE**

A paucity of data examines the effectiveness of cholinesterase inhibitors in moderate to severe Alzheimer's disease. Although 1 cholinesterase inhibitor has now been studied, these data were not published at the time of the evidence-based review for the American Academy of Neurology practice parameter.

Feldman et al.<sup>7</sup> examined the efficacy of donepezil in treating moderate to severe Alzheimer's disease. In their 24-week, double-blind, placebo-controlled trial, 290 patients with moderate to severe Alzheimer's disease were randomly assigned to receive either 5 mg/day of donepezil for 28 days and then increased to 10 mg/day thereafter (N = 144) or placebo. Moderate to severe Alzheimer's was defined as an MMSE score from 5 to 17 and an ADFACS score of ≤ 6. Outcome measures included the CIBIC-plus and the Severe Impairment Battery (SIB), which is similar to the ADAS-cog but is adapted to a population with severe illness. The study also assessed functional ability on the DAD and behavior on the NPI as discussed above.

Findings were consistent with trials that examined the effects of donepezil on mildly to moderately severe Alzheimer's disease.<sup>6,14</sup> Significant donepezil-placebo differences in the CIBIC-plus with caregiver input scores were found throughout the trial. Mean CIBIC-plus scores were above baseline severity for the donepezil-treated group until week 24. Placebo-treated group scores remained about the same for 12 weeks relative to baseline and drifted downward throughout the rest of the study. The difference between the drug-treatment group and the placebo group scores was significant from week 4 until the end of the trial.<sup>7</sup>

The SIB outcome measure revealed similar data (Figure 4).<sup>7</sup> There were mean SIB improvements in cognition in the donepezil-treated group that were significant versus placebo throughout the trial. Patients who received placebo remained virtually at baseline for 12 weeks and then began a decline that progressed about 3 points below baseline by the end of the 6-month study period. Patients who received donepezil improved almost 5 points above baseline by week 12 and maintained improvement throughout the remainder of the 6-month study. Although these patients were moderately to severely ill, they responded to the cholinesterase inhibitor much like patients in other studies who were not as severely ill. It is difficult to determine what might happen if the therapy had been continued beyond 6 months; however, there is no indication that the effect would have been abruptly lost.

## USE IN OTHER DISORDERS

Cholinesterase inhibitors have demonstrated efficacy in maintaining cognition and function and in stabilizing behavior in patients with mild to severe Alzheimer's disease. They have additionally been used to treat various other disorders. For example, placebo-controlled trials with these agents have examined their effectiveness in treating dementia with Lewy bodies<sup>11</sup> and vascular dementia.<sup>18,19</sup> Open trials and case reports have also reported on the effectiveness of cholinesterase inhibitors in treating conditions including multiple sclerosis,<sup>20</sup> Parkinson's disease dementia,<sup>21</sup> and bipolar disorder,<sup>22</sup> and as an adjunctive treatment for schizophrenia<sup>23</sup> and Wernicke-Korsakoff's syndrome,<sup>24</sup> among others.

## CONCLUSION

According to both short- and long-term studies, cholinesterase inhibitors have positive effects compared with placebo in the treatment of Alzheimer's disease— affecting cognition, function, and behavioral outcomes. They are effective in mild to moderate disease, and preliminary data suggest that this effect is mirrored in severe disease as well. Additionally, cholinesterase inhibitors may be beneficial in treating various non-Alzheimer dementias, and the agents in this class that are commonly in use are generally well tolerated.

There are limitations to these medications, however, because although stabilization occurs, there is typically only a modest improvement from baseline. Additionally, the effects are not sustained indefinitely, and the disease continues to progress even while patients are receiving treatment with cholinesterase inhibitors. Adverse events are manageable, and with careful titration, patients can tolerate increases quite well; however, side effects can include diarrhea, nausea, vomiting, dyspepsia, asthenia, dizziness, headache, weight loss, and even anorexia—sometimes to such an extreme that patients must discontinue treatment. Additional therapies for Alzheimer's disease need to be developed that include highly tolerable agents with alternative mechanisms of action and broader efficacy to delay disease onset, arrest the disease, or even reverse the progression of the disease entirely. Until these new therapies are developed, the cholinesterase inhibitors will remain important treatments for Alzheimer's disease.

*Drug names:* donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of her knowledge, donepezil, galantamine, and rivastigmine are not approved by the U.S. Food and Drug Administration for the treatment of severe Alzheimer's disease.

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