Therapeutic Class Overview
Alzheimer's Agents

Therapeutic Class

- **Overview/Summary:** Alzheimer's disease (AD) is a progressive disease that affects both cognition and behavior. AD is classified under Delirium, Dementia, and Amnestic and Other Disorders in the American Psychiatric Association's *Diagnostic and Statistical Manual for Mental Disorders*, Text Revision, 4th edition (DSM-IV-TR).[1] It is defined as the development of multiple cognitive deficits manifested by memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1] Pathophysiologic mechanisms behind the disease are not entirely understood, but a common pathologic finding is the accumulation of beta-amyloid proteins in the brain. Subsequently, inflammatory and free radical processes eventually result in neuron dysfunction and death. Although research is looking at preventing plaque formation or enhancing plaque removal, current drug therapies target symptom reduction and slow progression of cognitive and behavioral decline.

  The course of the disease starts with mild cognitive impairment, progresses to more severe effects and, eventually, death, commonly due to pneumonia or aspiration. Current pharmacotherapy is aimed at reducing the rate of cognitive decline. Options for pharmacotherapy include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. Behavioral conditions show some improvement with these agents but, once again, treatment is geared towards reducing symptoms instead of curing or arresting the disease.

  In the early 1980s, tacrine was the first drug evaluated as a means to enhance cholinergic activity in patients with AD. Due to an extensive adverse effect profile and risk of hepatotoxicity, tacrine has been discontinued and no longer available on the market as of 2012. Donepezil has specificity for inhibition of acetylcholinesterase compared to butyrylcholinesterase, which results in fewer side effects (e.g., nausea, vomiting and diarrhea) but may make it less effective in late stages of Alzheimer's disease since butyrylcholinesterase is more abundant than acetylcholinesterase in patients with late stages of the disease. Rivastigmine has central activity for acetylcholinesterase and butyrylcholinesterase, with low affinity at these sites in the periphery. The most recently approved cholinesterase inhibitor, galantamine, is specific for acetylcholinesterase and has activity as a nicotinic receptor modulator which results in acetylcholine binding more tightly to the receptor.

  The NMDA receptor antagonist memantine effects the transmission of glutamate by weakly and noncompetitively blocking cation channels on the glutamate neuron. This weak binding does not allow for chronic stimulation which may damage neurons but does allow for bursts of excitation allowing for appropriate signal transmission.[9] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of brain cells in AD patients. This agent appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional and global deterioration apparent in patients with moderate-to-severe AD.

  Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in AD. It is believed that the memory loss in AD is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an NMDA receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is Food and Drug Administration (FDA) approved only for moderate-to-severe dementia and the cholinesterase inhibitors are indicated for mild-to-moderate disease with the exception of donepezil which also is indicated for moderate-to-severe disease and rivastigmine which is indicated for severe dementia. Rivastigmine has the additional indication of dementia associated with Parkinson's disease.[6-7]

Table 1. Medications Included Within the Therapeutic Class Review[5-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Donepezil (Aricept®, Aricept ODT®)	Indicated for the treatment of mild, moderate and severe dementia of the Alzheimer's type	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg	-
Galantamine (Razadyne®*, Razadyne ER®)	Indicated for the treatment of mild-moderate dementia of the Alzheimer's type	Extended-release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg	✔
Memantine (Namenda®)	Indicated for the treatment of moderate-severe dementia of the Alzheimer's type	Solution: 10 mg/5 mL Tablet: 5 mg 10 mg 4 week titration pack	-
Rivastigmine (Exelon®, Exelon Patch®)	Indicated for the treatment of mild, moderate and severe dementia of the Alzheimer's type; indicated for the treatment of mild-moderate dementia associated with Parkinson's disease	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours	-

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- All cholinesterase inhibitors (donepezil, galantamine and rivastigmine) have the Food and Drug Administration (FDA)-approved indication for mild-to-moderate Alzheimer's disease (AD) while donepezil has the added indication for moderate-to-severe AD and rivastigmine for severe AD. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has Food and Drug Administration approval for moderate-to-severe dementia of AD. It has also been studied as add-on therapy with donepezil and galantamine with results suggesting better tolerability than monotherapy.[49-52, 60-63]
- A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate AD.[11-48] Use of donepezil, galantamine or rivastigmine in the treatment of cognitive

and neuropsychiatric complications of Alzheimer's disease provides comparable outcomes. Although the addition of memantine to any current cholinesterase regimen may confer additional benefit, particularly in the area of tolerability and caregiver burden the overall clinical impact of these agents are marginal.[74]

- Currently there are limited head-to-head trials comparing the efficacy of the cholinesterase inhibitors and no data comparing memantine to other agents used to treat AD to demonstrate clear clinical advantages of one agent over another. Better designed head-to-head studies are needed between these agents to fully evaluate their comparative efficacy. Efficacy data on cognitive function from trials comparing the cholinesterase inhibitors have shown that the cholinesterase inhibitors are equally effective. The British Association for Psychopharmacology has determined that all cholinesterase inhibitors have shown equal efficacy and differ only in frequency of side effects.[70]
- Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients. However, a review by Liepelt et al describes efficacy from donepezil similar to that of rivastigmine.[72] The Quality Standards Subcommittee of the American Academy of Neurology also reported comparable efficacy between rivastigmine and donepezil.[73]
- There is insufficient clinical evidence to conclude that one agent is safer or more efficacious than another.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[68-70]
    - Supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease (AD).
    - Memantine is effective in the treatment of moderate-to-severe AD.
    - Memantine may be added to a cholinesterase inhibitor.
- Other Key Facts:[5-9]
    - Currently galantamine is available generically.[4]
    - All agents with the exception of memantine are approved for mild-moderate AD.
        - Donepezil is also indicated moderate-severe AD and rivastigmine for severe AD.
        - Memantine is indicated for moderate-severe AD only.
        - Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients.
    - Rivastigmine is the single cholinesterase inhibitor not metabolized by the cytochrome P450 enzyme system.

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Alzheimer's Agents

Overview/Summary

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The course of the disease starts with mild cognitive impairment, progresses to more severe effects and, eventually, death, commonly due to pneumonia or aspiration. Predictors of mortality include severity at time of diagnosis, abnormal neurologic findings, and the presence of heart disease and diabetes.[2] AD is the most common of the dementias in the United States, accounting for more than 50% of all diagnosed dementias. It is estimated that in 2007 there were 5.1 million Americans with AD.[3]

By 2050, one in five people will be over age 65 years, and the number of Alzheimer's patients is projected to be 11-16 million.[4] Although there is no definitive diagnostic laboratory, clinical or imaging tests available, neuropsychological testing and clinical evaluation is 90% accurate. Treatment consists of nonpharmacologic and pharmacologic therapies, with nonpharmacologic interventions as the primary mechanism for management of memory loss and behavioral symptoms of AD. Nonpharmacologic therapies consist of keeping a notepad in one's pocket to make reminders, posting lists and notes throughout the house, exercising one's brain through reading and crossword puzzles, and other strategies. Current pharmacotherapy is aimed at reducing the rate of cognitive decline. Options for pharmacotherapy include cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. Behavioral conditions show some improvement with these agents but, once again, treatment is geared towards reducing symptoms instead of curing or arresting the disease.

In the early 1980s, tacrine was the first drug evaluated as a means to enhance cholinergic activity in patients with AD. Due to an extensive adverse effect profile and risk of hepatotoxicity, tacrine has been discontinued and is no longer available on the market as of 2012. Donepezil has specificity for inhibition of acetylcholinesterase compared to butyrylcholinesterase, which results in fewer side effects (eg, nausea, vomiting and diarrhea) but may make it less effective in late stages of Alzheimer's disease since butyrylcholinesterase is more abundant than acetylcholinesterase in patients with late stages of the disease. Rivastigmine has central activity for acetylcholinesterase and butyrylcholinesterase, with low affinity at these sites in the periphery. The most recently approved cholinesterase inhibitor, galantamine, is specific for acetylcholinesterase and has activity as a nicotinic receptor modulator which results in acetylcholine binding more tightly to the receptor.

The NMDA receptor antagonist memantine effects the transmission of glutamate by weakly and noncompetitively blocking cation channels on the glutamate neuron. This weak binding does not allow for chronic stimulation which may damage neurons but does allow for bursts of excitation allowing for appropriate signal transmission.[9] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of brain cells in AD patients. This agent appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional and global deterioration apparent in patients with moderate-to-severe AD.

Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in AD. It is believed that the memory loss in AD is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an NMDA receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is Food and Drug Administration (FDA) approved only for moderate-to-severe dementia and the cholinesterase inhibitors are indicated for mild-to-moderate disease with the exception of donepezil which also is indicated for moderate-to-severe disease and rivastigmine which is indicated for severe dementia. Rivastigmine has the additional indication of dementia associated with Parkinson's disease.[6-7]

Medications

Table 1. Medications Included Within Class Review[5-9]

Generic Name (Trade name)	Medication Class	Generic Availability
Donepezil (Aricept®, Aricept ODT®)	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors	-
Galantamine (Razadyne®, Razadyne ER®)	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors	✔
Memantine (Namenda®)	N-methyl-D-aspartate (NMDA) Receptor Antagonist	-
Rivastigmine (Exelon®, Exelon Patch®)	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors	-

*Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[5-9]

Generic Name	Mild-to-Moderate Dementia of the Alzheimer's Type	Moderate-to-Severe Dementia of the Alzheimer's Type	Severe Dementia of the Alzheimer's Type	Mild-to-Moderate Dementia Associated with Parkinson's Disease
Donepezil	✔	✔		
Galantamine	✔			
Memantine		✔		
Rivastigmine	✔		✔	✔

Potential off-label uses for donepezil include autism, vascular dementia, poststroke aphasia and improvement of memory in multiple sclerosis patients. Rivastigmine capsules have been used off-label for the treatment of the behavioral symptoms in Lewy-body dementia.[10]

Pharmacokinetics

The pharmacokinetic parameters for each of the agents in this class vary in some respects. Galantamine and donepezil are metabolized primarily by cytochrome P450 (CYP) 2D6 and 3A4. Rivastigmine is metabolized by plasma esterases and not the CYP group of isoenzymes.[5-8]

Galantamine extended release (ER) is galantamine hydrochloride encased in a slow-release capsule. The pharmacokinetics of the two delivery methods are equal except for the time to maximum concentration, which occurs later, and peak levels, which are lower with the ER version. The clinical significance of this difference is not known.[5-8]

Table 3. Pharmacokinetics[5-9]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Donepezil	100	CYP2D6 and CYP3A4,	Renal (57)	2; not	70

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
		and glucuronidation		specified	
Galantamine	90	CYP2D6 and CYP3A4, and glucuronidation	Primarily renal	None reported	7
Memantine	Highly absorbed	Hepatic, partially	Renal (48) unchanged in urine	3 with minimal activity	60 to 80
Rivastigmine	36 to 40	Cholinesterase-mediated hydrolysis	Renal (90-97)	NAP226-90 (minimal)	1.5 (3 hours after patch removal)

Clinical Trials

Until recently, there were no head-to-head trials comparing the efficacy of the different agents used to treat Alzheimer's disease (AD). Limited comparative data is now available. Kaduszkiewicz et al[11] conducted a systematic review of all randomized-controlled trials of donepezil, rivastigmine and galantamine published from 1989-2004. They found 22 trials which met the inclusion criteria: 12 for donepezil, 5 for rivastigmine and 5 for galantamine. The authors found that the differences in efficacy among the 3 medications vary by study and that the overall efficacy vs placebo is moderate. They concluded that "the scientific basis for recommendations of the cholinesterase inhibitors for AD is questionable."

Although data evaluating AD treatments and their impact on physician services utilizations is limited. Literature is available on AD and utilization of services. One study by Fillenbaum et al looked at the probability and frequency of outpatient visits of patients with AD and assessed whether stage of illness or institutionalization had any impact.[12] In this Medicare population, the number of patients with AD and a Medicare-reimbursed outpatient visit ranged from 81 to 95% and was not related to stage of dementia or institutional status.[12] Whether AD patients compared to those without AD have more physician visits has not been clearly determined due to questions about diagnosis and identification on claims. Another study showed the onset of AD is not associated with greater use of acute care services nor is the high use of nursing home care offset by fewer emergency room or hospital encounters.[13] Another study evaluated a care consultation multicomponent telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[14] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission and had decreased depression and strain.

A recent study still unpublished at the time of this review for rivastigmine transdermal was conducted in patients with severe AD. The ACTION study, a 24-week, prospective, randomized, parallel-group, double-blind, study compared the 13.3 mg/24 hour strength to the 4.6 mg/24 hour patch in severe AD, demonstrating significantly less deterioration with the13.3 mg/24 hour patch at weeks 16 and Week 24 in activities of daily living decline and significantly less cognition . The overall incidence of adverse events was comparable between the 13.3 mg/24 h and Exelon Patch 4.6 mg/24 h groups (74.6 vs. 73.3%). The most common adverse events were psychiatric disorders and skin and subcutaneous tissue disorders.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alzheimer's Disease				
Geldmacher et al[15] Donepezil 5 mg/day; treatment duration varied	Observational Follow-up of patients previously enrolled in one of three randomized, double-blind, placebo-controlled trials of donepezil, and two subsequent open-label studies	N=1,115 Duration not specified	Primary: Time to nursing home placement Secondary: Not reported	Primary: Use of donepezil of 5 mg/day or more was associated with significant delays in nursing home placement. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. When donepezil was taken at effective doses for at least 9 to 12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement. Secondary: Not reported
Courtney et al[16] Donepezil 5 to 10 mg/day vs placebo	DB, R Patients with Alzheimer's disease	N=565 12 week run-in period; 156 weeks total duration	Primary: MMSE, BADLS, time to entering institution Secondary: Not reported	Primary: Cognition averaged 0.8 MMSE points better (95% CI, 0.5 to 1.2; *P*<0.0001) and functionality 1.0 BADLS points better (0.5 to 1.6; *P*<0.0001) with donepezil over the first two years. No significant benefits were seen with donepezil compared to placebo in institutionalization (42 vs 44% at three years; *P*=0.4) or progression of disability (58 vs 59% at three years; *P*=0.4). The relative risk of entering institutional care in the donepezil group compared to placebo was 0.97 (95% CI, 0.72 to 1.30; *P*=0.8); the relative risk of progression of disability or entering institutional care was 0.96 (95% CI, 0.74 to 1.24; *P*=0.7). No significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, adverse events or deaths, or between 5 and 10 mg donepezil. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Birks and Harvey[17] Donepezil 5 to 10 mg/day vs placebo	MA (24 trials) Patients diagnosed with Alzheimer's disease	N=5,796 12 to 60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: Statistically significant difference was seen on the ADAS-Cog scale for patients treated with donepezil 5 mg at 24 weeks (WMD, -2.02 points; 95% CI, –2.77 to –1.26; *P*<0.00001) and 10 mg at 24 weeks (WMD, –2.81 points; 95% CI, –3.55 to –2.06; *P*<0.00001). Statistically significant difference was seen on the MMSE for patients treated with donepezil 10 mg/day as compared to placebo at 52 weeks (WMD, 1.84 points; 95% CI, 0.53 to 3.15; *P*=0.006). Global Clinical State, CIBIC-Plus scores showed significant benefit to patients treated with donepezil 5 and 10 mg/day (OR, 2.38; 95% CI, 1.78 to 3.19; *P*<0.00001, and OR, 1.82; 95% CI, 1.42 to 2.35; *P*<0.00001). Improvements were seen in ADL scores for patients in the donepezil group over those in the placebo group (*P*<0.01 for all scales used). Significantly more patients treated with donepezil 10 mg/day withdrew from treatment (24 vs 20%; *P*=0.003); however, there was no difference in withdrawal rates between the 5 mg/day and placebo group (*P*=0.56). Adverse events that occurred significantly more frequently in both the 5 and 10 mg/day treatment groups as compared to placebo are: anorexia, diarrhea and muscle cramps. Secondary: Not reported
Black et al[18] Donepezil 5 mg daily for 6 weeks, then 5 mg twice a day (10 mg daily) for 18 weeks thereafter	DB, MC, PC, RCT Men or women aged at least 50 years who were ambulatory or ambulatory-aided (cane, walker or	N=343 24 weeks	Primary: SIB (lower scores indicating greater impairment); CIBIC-Plus (lower scores indicating	Primary: Donepezil was more efficacious when compared to placebo on SIB score change from baseline to endpoint, as well as on CIBIC-Plus score (*P*≤0.05 for all results). Secondary: On the ADCS-ADL-sev, both the donepezil group and the placebo group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	wheelchair) diagnosed with probable Alzheimer's disease consistent with the DSM-IV and the NINCDS-ADRDA criteria, MMSE score between 1 and 12 (inclusive), a modified Hachinski Ischemic score of ≤6, and a FAST score of ≥6		improvement) Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	declined from baseline, and the treatment difference was not significant (*P*=0.3574). On the NPI, donepezil was not significantly different from placebo (*P*=0.4612). The donepezil group showed significant improvement from screening to endpoint on the MMSE compared to placebo (*P*=0.0267). The CBQ stress measure showed no significant change from baseline for either group (*P* value not reported). The RUSP scores also had low average responses with little movement from baseline and no significant differences (*P* value not reported).
Winblad et al[19] Donepezil 5 mg for the first 30 days followed by daily donepezil 10 mg (or 5 mg if not well tolerated) for the next 5 months vs placebo	DB, PC, PG Patients 50 years or older with the ability to walk alone or with help, a MMSE score of 1-10, and a FAST rating of stage 5 (requires assistance in choosing proper clothing) to 7c (non-ambulatory-unable to walk without assistance), a diagnosis of probable or possible Alzheimer's disease consistent with the DSM-IV and the criteria of the NINCDS-ADRDA	N=248 6 months	Primary: Change from baseline to month 6 in the scores for the SIB and the Modified ADCS-ADL-severe Secondary: Change in scores at 6 months compared to screening for the MMSE baseline for the NPI, and scores at month 6 for the CGI-I	Primary: At six months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo on both SIB and ADCS-ADL-severe (all *P*<0.05). Secondary: CGI-I scores and the mean change from screening scores on the MMSE at six- month follow-up favored donepezil treatment over placebo (all *P*<0.05). There was no significant difference between treatment groups on the NPI for the modified intention-to-treat population (*P*=0.43).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Winblad et al[20] Donepezil 5 mg daily for the first 28 days and 10 mg/day thereafter, as per clinician's judgment for the next 11 months vs placebo All patients entering the 2-year, open-label phase receiving 5 mg of donepezil, once daily for the first 28 days, after which the dosage was increased to 10 mg/day, as per clinician's judgment.	DB, OL, PC Men and women aged between 40 and 90 years with a diagnosis of Alzheimer's disease consistent with the DSM-IV criteria and the NINCDS-ADRDA criteria for possible or probable Alzheimer's disease	N=286 52 week, randomized, double-blinded, placebo-controlled phase plus a 2-year, open-label continuation phase for a total of 3 years	Primary: GBS Secondary: MMSE, GDS, PDS, NPI	Primary: The GBS total scores indicate that both the continuous-treatment group and delayed-start groups had declined, with the difference between the two groups favoring the continuous-donepezil group, over the three-year period (*P*=0.056). Secondary: The MMSE declined significantly less in the continuous-treatment group than in the delayed-start group over the course of the study (*P*=0.004, *P*=0.057, respectively). GDS declined significantly less over the three-year study period in patients in the continuous-treatment group than in those in the delayed-start group (*P*=0.0231). There was a trend favoring continuous-donepezil treatment over delayed-start treatment on the PDS, although it was not statistically significant (*P*=0.091). NPI results showed no significant treatment differences between the groups (*P* value not reported).
Wallin et al[21] Donepezil 5 to 10 mg/day vs historical data	MC, PRO Patients 40 years of age and older with diagnosis of dementia and probable Alzheimer's disease	N=435 3 years	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE (higher score=better function) patients had a mean score of 22.0±4.6 at baseline and 19.1±7.3 at 36 months. After 36 months of donepezil treatment, the mean decline was 3.8 points (95% CI, 3.0 to 4.7). For ADAS-Cog (higher score=lower function) patients had a mean score of 20.7±10.0 at baseline and 26.1±16.4 at 36 months. After 36 months, the mean increase was 8.2 points (95% CI, 6.4 to 10.0). A modeling equation predicts an increase in ADAS-Cog to be 4-9 points in 12 months without treatment. Scores for the treatment group were significantly better than predicted scores for nontreatment (95% CI, 14.5 to 16.6). For CIBIC, at two months, 34% of patients were considered improved, 59% unchanged and 7% were worse. At six months, 28% of patients were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				considered improved, 46% unchanged and 26% were worse. At 12 months, 20% of patients were considered improved, 29% unchanged and 51% were worse. At 36 months, 30% of patients were considered improved or unchanged. The IADL change from baseline at 6 months was 1.01±3.62, at 12 months 2.19±4.45 and at 36 months 6.18±5.54. Secondary: Not reported
Rogers et al[22] Donepezil 5 mg daily vs donepezil 10 mg daily vs placebo	DB, MC, PC, R Patients with mild-moderate Alzheimer's disease	N=473 24 weeks	Primary: ADAS-Cog, CIBIC Secondary: Not reported	Primary: Out of 473 patients, 80% of placebo patients, 85% of 5 mg patients and 68% of 10 mg patients completed the study. Those that discontinued due to adverse effects were 7, 6 and 16% in the placebo, 5 and 10 mg groups, respectively. Primary outcome measure was mean change in scores from baseline to endpoint in the ADAS-Cog. Both donepezil doses were statistically better than placebo (P<0.0001). Global functioning as measured by the CIBIC plus were statistically better for both donepezil groups compared to placebo at endpoint (P<0.005). Donepezil 5 and 10 mg treatment showed no statistical difference in improvements. Secondary: Not reported
Raskind et al[23] Galantamine 24 mg/day vs placebo	DB, PC, R Patients with mild-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Rockwood et al[24] Galantamine 24 mg/day	MC, OL Patients with Alzheimer's disease who had received galantamine treatment for up to 36 months	N=240 Up to 48 months	Primary: ADAS-Cog, DAD, adverse events Secondary: Not reported	Primary: Mean ADAS-Cog worsened from 22.6±8.6 at baseline to 31.3±13.1 at 48 months. DAD worsened from 73.4±18.1 at baseline to 36.1±29.0 at 48 months. Fifty one patients withdrew form the study. Secondary: Not reported
Cummings et al[25] Galantamine 8, 16 or 24 mg/day vs placebo	DB, PC, R Patients with mild-moderate Alzheimer's disease	N=978 21 weeks	Primary: NPI, caregiver distress related to patients' behavior Secondary: Not reported	Primary: NPI scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in NPI scores. Behavioral improvement in patients symptomatic at baseline ranged from 29 to 48%. Changes were evident in patients receiving 16 and 24 mg/day of galantamine. High-dose galantamine was associated with a significant reduction in caregiver distress. Secondary: Not reported
Loy and Schneider[26] Galantamine 8 to 36	MA (10 trials) Patients diagnosed	N=6,805 12 weeks-2	Primary: CIBIC-plus, ADAS-Cog,	Primary: Statistically significant difference was seen on the global rating scales for patients treated with galantamine, at all durations and all doses but 8

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day vs placebo	with mild cognitive impairment or Alzheimer's disease	years	ADCS-ADL, DAD, NPI Secondary: Not reported	mg/day (*P* values varied). Statistically significant difference was seen on the ADAS-Cog scale for patients treated with galantamine at all doses, with greater effect at six months than three months (*P* values varied). When reported, ADCS-ADL, DAD and NPI scores for patients treated with galantamine were significantly improved over those in the placebo group (*P* values not reported). Secondary: Not reported
Wilcock et al[27] Galantamine 24 mg vs galantamine 32 mg vs placebo	DB Patients with mild-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Both doses of galantamine were statistically better than placebo in the mean change in ADAS-Cog from baseline to endpoint (*P*<0.0001). Patients taking galantamine 24 mg had a -0.5 point mean change on the ADAS-Cog scale, while the 32 mg group had a -0.8 change. This compares to a +2.4 change for the placebo group. Statistical comparisons between the 24 mg group and the 32 mg group were not conducted. Discontinuations due to adverse events were 9%, 14% and 22% in the placebo, 24 and 32 mg dose groups, respectively. Secondary: Not reported
Dunbar et al[28] Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day	Post hoc analysis, DB, MC, PC, R Patients with mild-to-moderate probable Alzheimer's disease according to NINCDS/ADRDA	N=965 7 months	Primary: Nausea and vomiting Secondary: Not reported	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group and 5.0% of placebo group. Vomiting reports were as follows: 6.6% of the galantamine ER groups, 8.6% of the galantamine IR group and 2.2% of the placebo group. During dose titration, the area under the curve of daily percentage of patients reporting nausea or vomiting was significantly higher in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				galantamine IR group compared to placebo (320.9 vs 102.9; *P*=0.01) but for galantamine ER vs placebo and galantamine ER vs galantamine IR no significant differences were seen ([173.5 vs 102.9; *P*=NS], [320.9 vs 173.5; *P*=NS]). The mean daily nausea rate and the mean daily vomiting rate for galantamine ER and galantamine IR were not significantly different but when both were compared to placebo, significance was seen (*P*<0.05). The galantamine IR had a greater mean percentage of days with nausea compared to galantamine ER (38 vs 18.4%; *P*=0.014) while there was no significance for both galantamine groups compared to placebo. Secondary: Not reported
Brodaty et al[29] Galantamine 8 to 16 or 24 mg/day vs galantamine PRC 8 to 16 or 24 mg/day vs placebo	AC, DB, MC, PC, PG, R Patients with mild-to-moderate probable Alzheimer's disease according to NINCDS/ADRDA	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary: ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog/ memory, ADAS-Cog	Primary: Compared to placebo, galantamine PRC was significantly more effective with improvement from baseline in ADAS-cog/11 scores (OC mean change, 1.3 and -1.4, respectively; *P*<0.001; 95% CI, –3.74 to –1.68; LOCF mean change, 1.2 and -1.3, respectively; *P*<0.001; 95% CI, –3.34 to –1.49). Galantamine also showed similar results when compared to placebo (OC mean change, –1.8 and 1.3, respectively; *P*<0.001; 95% CI, –4.17 to –2.08; LOCF mean change, –1.6 and 1.2, respectively; *P*<0.01; 95% CI, –3.70 to –1.86). Secondary: ADCS-ADL scores were significantly improved in the galantamine PRC group vs placebo (OC; *P*=0.003; 95% CI, 0.85 to 4.03; LOCF; *P*<0.001; 95% CI, 1.09 to 3.91). The OC analysis was numerically better in treatment response while the LOCF analysis was statistically better for the galantamine group compared to placebo (OC; *P*=0.088; 95% CI, –0.21 to 2.99; LOCF; *P*=0.018; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.22 to 3.04). In galantamine PRC and galantamine groups vs placebo, OC NPI scores were not statistically significant but instead numerically significant (OC; *P*=0.451; 95% CI, –2.77 to 1.23; LOCF; *P*=0.941; 95% CI, –1.85 to 1.82), (OC; *P*<0.205; 95% CI, –3.31 to 0.71; LOCF; *P*<0.102; 95% CI, –3.42 to 0.23). Statistical significance was found in cognition improvement from baseline for both galantamine groups compared to placebo based on ADAS-cog/13, non-memory ADAS-Cog, and memory ADAS-Cog scores.
Burns et al[30] Rivastigmine	RETRO Patients with moderately severe Alzheimer's disease/dementia	N=2,126 3 trials, each 6 months	Primary: Effectiveness Secondary: Not reported	Primary: Mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (*P*<0.001). Clinical benefits were also observed with the MMSE, the six-item progressive deterioration scale, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the relative risk of dropping out due to adverse events was lower than in subjects with milder Alzheimer's disease. Secondary: Not reported
Birks et al[31] Rivastigmine 6 to 12 mg/day vs placebo	MA (8 trials) Patients diagnosed with Alzheimer's disease	N=3,660 12 to 52 weeks	Primary: ADAS-Cog, ADL, adverse events Secondary: Not reported	Primary: Statistically significant differences were seen in patients treated with rivastigmine at doses of 6 to 12 mg/day as compared to placebo for the following outcomes: ADAS-Cog (WMD, -2.09; 95% CI, –2.65 to –1.54) and ADL (WMD, -2.15; 95% CI, –3.16 to –1.13). At 26 weeks, 55% of patient had severe dementia in the rivastigmine group as compared to 59% in the placebo group (OR, 0.78; 95% CI, 0.64 to 0.94). Adverse events (nausea, vomiting, diarrhea, anorexia, headache, syncope,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				abdominal pain and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Rosler et al[32] Rivastigmine 1 to 4 mg/day vs rivastigmine 6 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients 50 to 85 years of age and not able to bear children, all patients met criteria for Alzheimer's type dementia as described in the DSM-IV and criteria for probable Alzheimer's disease according to criteria of the NINCDS/ADRDA, baseline MMSE 10-26	N=725 Dose titration over the first 12 weeks with a subsequent assessment period of 14 weeks, total of 26 weeks	Primary: Improvements in cognitive function and overall clinical status measured by the ADAS-Cog, CIBIC, PDS, MMSE and GDS Secondary: Safety and tolerability	Primary: Significant improvement in cognitive function assessed by the ADAS-Cog was observed with the higher dose group by ≥4 points compared to placebo (P<0.05). At week 26, significantly more patients in both rivastigmine groups had improved in global function as assessed by the CIBIC compared to those in the placebo group (P<0.05). Mean scores on the PDS improved from baseline in the higher dose group but fell in the placebo group (P<0.05). At week 26, mean scores in the MMSE and the GDS significantly improved in patients receiving rivastigmine 6-12 mg/day (P<0.05). Secondary: Discontinuation rates for any reason were significantly higher in the higher dose group than in the lower dose or placebo group (33% vs 14%). Adverse events related to treatment including nausea, vomiting, diarrhea, abdominal pain and anorexia, were generally mild and occurred most frequently during the dose escalation phase (23% in higher dose group, 7% in lower dose group and 7% in placebo group).
Winblad et al[33] Rivastigmine patch groups were up-titrated from a 5 cm² starting dose in 5 cm² steps to a maximum size of 20	DB, DD, MC, PG Women or men 50 to 85 years of age with a diagnosis of dementia of the Alzheimer's type	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI for	Primary: Patients receiving rivastigmine patches or capsules showed significant benefits compared to placebo at week 24 on the ADAS-Cog subscale (P<0.05 vs placebo for all rivastigmine groups). Treatment differences on the ADCS-CGIC were statistically significant for the 10 cm² patch and capsule group (all P<0.05 vs placebo). The 20 cm²

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cm² (target doses of 10 cm² or 20 cm² rivastigmine patch) vs rivastigmine capsule groups were up-titrated from 3 mg/day in steps of 3 mg/day to a maximum of 12 mg/day (target dose of 12 mg/day) vs placebo	according to the DSM-IV, and probable Alzheimer's disease according to the criteria of the NINCDS/ ADRDA, and MMSE scores of 10 to 20 inclusive		behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive functions; Trail Making Test Part A for assessment of attention, visual tracking and motor processing speed	patch did not achieve statistical significance compared to placebo in the analysis (*P*=0.054). Secondary: Rivastigmine patches and capsule provided statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test A (all *P*<0.05 vs placebo). Changes from baseline on the NPI, NPI-distress subscale, and Ten-point Clock-drawing Test in the rivastigmine groups were not significantly different from those in the placebo groups (all *P*>0.05).
Winblad et al[34] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs	DD, PC, RCT Patients 50 to 85 years of age with MMSE scores of 10 to 20 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=1,195 Dose titration in 4-week intervals over 16 weeks and maintained at their highest well-tolerated dose for a further 8 weeks, total of 24 weeks	Primary: ADAS-Cog subscale (assess orientation, memory, language, visuospatial and praxis function), ADCS-CGIC (assess single global rating) Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making	Primary: Patients in all rivastigmine groups (patch and capsule) showed significant improvements compared to placebo at week 24 with respect to ADAS-Cog and the ADCS-CGIC (all *P*<0.05 vs placebo). Secondary: All rivastigmine groups (patch and capsule) showed statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test part A (all *P*<0.05 vs placebo). Statistically significant treatment effects were not attained on the NPI or Ten Point Clock-drawing Test (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Test part A	
Blesa et al[35] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs placebo	DB, DD, PC Active controls included different size rivastigmine patches and rivastigmine capsules, caregiver preference based on data generated during the IDEAL trial (Winblad et al)	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (*P*<0.0001). 70% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 55% of caregivers preferred the patch due to ease of use (*P*=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (*P*<0.0001). 74% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 64% of caregivers preferred the patch due to ease of use (*P*<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (*P*<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (*P*<0.0001), greater satisfaction with administration (*P*<0.0001), less interference with daily life with the patch than the capsule (*P*<0.01). Secondary: Not reported
Winblad, Kawata et al[36] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily	DB, DD, PC Active controls included different size rivastigmine patches and rivastigmine capsules	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (*P*<0.0001). 70% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 55% of caregivers preferred the patch due to ease of use (*P*=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (*P*<0.0001). 74% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 64% of caregivers preferred the patch due to ease of use (*P*<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (*P*<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (*P*<0.0001), greater satisfaction with administration (*P*<0.0001), less interference with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				daily life with the patch than the capsule (*P*<0.01). Secondary: Not reported
Cummings et al[37] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 15 cm^2 rivastigmine patch (13.3 mg/24 hours)	DB, PG. RCT Patients 50 to 85 years of age with MMSE scores of 10 to 24 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=567 48 weeks	Primary: ADCS-IADL scale and ADAS-cog Secondary: Time to functional decline on the ADCS-IADL, change in the Trail Making Test parts A and B (TMT-A and TMT-B), and change in the 10-item Neuropsychiatric Inventory (NPI-10), and the NPI-caregiver distress scale.	Primary: The 13.3 mg/24 h patch was statistically superior to the 9.5 mg/24 h patch on the ADCS-IADL scale from week 16 (*P*=0.025) onwards including week 48 (*P* = 0.002), and ADAS-cog at week 24 (*P*= 0.027), but not at week 48 (*P* = 0.227). Secondary: Functional decline on the ADCS-IADL tended to occur later in the 13.3 mg/24 h patch group than in the 9.5 mg/24 h patch group, but the observed difference did not reach significance. Proportion of patients with functional decline was 77.0% in the 13.3 mg/24 h patch group compared to 81.2% with the 9.5 mg/24 h patch Group. The difference was not statistically significant. Patients in the 13.3 mg/24 h patch group had smaller increases in time to complete the TMT-A at weeks 24 and 48 compared to those in the 9.5 mg/24 h patch group, but the observed difference did not reach significance. Differences were not significantly different in changes in the change in the 10-item (NPI-10), and the NPI-caregiver distress scale. The most frequently reported adverse events by primary system organ class were GI disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 h patch, respectively), psychiatric disorders (25.4 vs. 21.6%, respectively) and nervous system disorders (21.4 vs. 18.4%, respectively). Skin and subcutaneous tissue disorders were less frequently observed with the 13.3 mg/24 h than the 9.5 mg/24 h patch (2.1 vs 6%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Harry et al[38] Donepezil with doses ranging from 5 to 10 mg/day or galantamine with doses ranging from 8 to 36 mg/day vs placebo	MA Patients with mild-to-moderate Alzheimer's disease, and without diagnosis of any other psychiatric or neurological disorder	N=3,353 3 donepezil studies 5 galantamine studies Duration varied	Primary: ADAS-Cog or MMSE Secondary: Not reported	Primary: The majority of patients showed no difference compared to placebo. There was no significant difference in efficacy between the groups. Secondary: Not reported
Klatte et al[39] Donepezil at least 5 mg and vitamin E at least 1,000 IU	RETRO Patients with Alzheimer's disease; data was compared to the Consortium to Establish a Registry for Alzheimer's disease database for patients collected prior to the availability of these treatment options	N=130 1 year	Primary: MMSE Secondary: Not reported	Primary: Patients declined at a significantly lower rate as compared to the Consortium to Establish a Registry for Alzheimer's disease data. Secondary: Not reported
Wilcock et al[40] Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, R Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL, MMSE, ADAS-Cog, NPI Secondary: Not reported	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. In terms of cognition, galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The between group difference in MMSE change, which showed a trend for increased effectiveness of galantamine, did not reach statistical significance. In the ADAS-Cog analysis, between group differences for the total population were not significant, whereas galantamine treated patients with MMSE scores of 12-18 demonstrated an increase (worsening) in the ADAS-Cog score of 1.61+/-0.80 vs baseline, compared to an increase of 4.08+/-0.84 for patients treated with donepezil. More caregivers of patients receiving galantamine reported reductions in burden compared to donepezil. Changes from baseline in NPI were similar for both treatments. Secondary: Not reported
Jones et al[41] Donepezil up to 10 mg every day vs galantamine up to 12 mg twice a day	OL, R Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily living Secondary: Not reported	Primary: Physicians and caregivers reported statistically significant greater satisfaction/ease of use with donepezil compared to galantamine at weeks four and 12. Significantly greater improvements in cognition were observed for donepezil vs galantamine on the ADAS-Cog at week 12 and at endpoint. Activities of daily living improved significantly in the donepezil group compared to the galantamine group at weeks four and 12 (P<0.05). 46% of galantamine patients reported gastrointestinal adverse events vs 25% of donepezil patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wilkinson et al[42] Donepezil up to 10 mg every day vs rivastigmine up to 6 mg twice a day	OL, R Patients with mild-moderate Alzheimer's disease	N=111 12 weeks	Primary: ADAS-Cog, tolerability Secondary: Not reported	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; *P*=0.009). 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. Both groups showed comparable improvements in ADAS-Cog administered at weeks four and 12. Secondary: Not reported
Mossello et al[43] Donepezil 5 to 10 mg vs galantamine 16 to 24 mg vs rivastigmine 6 to 12 mg	OL, OS Patients with mild-to-moderate Alzheimer's disease; 63% were taking donepezil, 32% were taking rivastigmine, and 5% were taking galantamine	N=407 9 months (212 patients completed all 9 months)	Primary: MMSE, ADL and IADL Secondary: Not reported	Primary: There were no differences amongst the three groups in regards to any of the outcome measures (galantamine was not included in the MMSE comparison due to the small number of treated subjects). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; *P*=0.01) and vs galantamine (21%; *P*=0.01). Secondary: Not reported
Aguglia et al[44] Donepezil vs galantamine	OL Patients in Italy diagnosed with Alzheimer's disease	N=242 6 months	Primary: MMSE, ADAS-Cog, ADL and IADL Secondary: Not reported	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the three groups. There were no differences on changes in the IADL measure among the three groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs rivastigmine				In the ADL measure, donepezil and galantamine patients showed a decrease while there was no change for rivastigmine patients. Rivastigmine showed a small numerical advantage (but not statistically) compared to donepezil and galantamine on the ADAS-Cog. Secondary: Not reported
Lopez-Pousa et al[45] Donepezil average dose 5.87 mg/day vs galantamine average dose 14.81 mg/day vs rivastigmine average dose 6.41 mg/day vs 45 historical controls	OL, PRO with historical controls Patients with mild-moderate Alzheimer's disease over 6 months	N=147 6 months	Primary: MMSE Secondary: Not reported	Primary: All 3 treatment groups had better MMSE scores compared to control (donepezil; *P*<0.001, galantamine; *P*<0.01, and rivastigmine; *P*<0.03). There were no statistical differences between the groups on measures of cognitive decline (via MMSE). Secondary: Not reported
Trinh et al[46] Cholinesterase inhibitors (donepezil, eptastigmine*, galantamine metrifonate*, physostigmine patch*, rivastigmine, tacrine,	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one month with a cholinesterase	29 trials Duration varied	Primary: NPI, ADAS-noncog, ADL and IADL Secondary: Not reported	Primary: Cholinesterase inhibitors improved the NPI statistically better than placebo (95% CI, 0.87 to 2.57). Cholinesterase inhibitors improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI, 0.0 to 0.05). Cholinesterase inhibitors improved ADL numerically but not significantly better than placebo (95% CI, 0.0 to 0.19).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
velnacrine*) vs placebo	inhibitor			Cholinesterase inhibitors improved IADL statistically compared to placebo (95% CI, 0.01 to 0.17). Secondary: Not reported
Lanctot et al[47] Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) vs placebo	MA Adult patients diagnosed with Alzheimer's disease	N=7,954 16 trials that varied in duration	Primary: Global responders, using CGI-C, CIBIC, adverse, events, dropouts Secondary: Not reported	Primary: For cholinesterase inhibitors the pooled mean proportion of global responders was in excess by 9% when compared to the placebo treatment (9%; 95% CI, 6 to 12). In the cholinesterase inhibitor treatment groups the rates of adverse events, dropout for any reason and dropout because of adverse events were higher compared to the placebo treatment groups (8%; 95% CI, 5 to 11; 8%; 95% CI, 5 to 11; and 7%; 95% CI, 3 to 10). The number needed to treat for one additional patient to benefit was 7 (95% CI, 6 to 9) for stabilization or better, 12 (95% CI, 9 to 16) for minimal improvement or better and 42 (95% CI, 26 to 114) for marked improvement. The number needed to treat for one additional patient to experience an adverse event was 12 (95% CI, 10 to 18). Secondary: Not reported
Birks et al[48] Donepezil 10 mg/day or galantamine 24 mg/day in two doses or rivastigmine 6-12 mg/day in 2 doses vs	MA Patients diagnosed with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 Minimum 6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals prior	*Cholinesterase inhibitor vs placebo (12 trials)* Primary: Significant benefit was seen in CIBIC-Plus for patients treated with a cholinesterase inhibitor over placebo; more patients were scored as "showed improvement" than "showed decline/no change" (OR, 1.56; 95% CI, 1.32 to 1.85; *P*<0.00001): eight studies. No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at one year (*P* value not reported): one trial.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			to six months, adverse events	Significant improvement in ADAS-Cog was found for patients treated with donepezil, galantamine, or rivastigmine over placebo (WMD, –2.66; 95% CI, –3.02 to –2.31; *P*<0.00001): 10 studies. Significant benefit was seen in MMSE for patients treated with a cholinesterase inhibitor over placebo (WMD, 1.37; 95% CI, 1.13 to 1.61; *P*<0.00001): nine studies. Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (WMD, 2.40; 95% CI, 1.55 to 3.37; *P*<0.00001 for PDS; and WMD, 4.39; 95% CI, 1.96 to 6.81; *P*=0.0004 for DAD). Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (WMD, –2.44; 95% CI, –4.12 to –0.76; *P*=0.004). Secondary: Significantly more patients treated with a cholinesterase inhibitor (29%) withdrew prior to six months than those in the placebo groups (18%; *P*<0.00001). Adverse events that occurred significantly more frequently in the cholinesterase inhibitor group than the placebo group, from pooled data from at least 6 trials included: abdominal pain, anorexia, dizziness, diarrhea, headache (*P*<0.0001), insomnia (*P*=0.007), nausea, vomiting (*P*<0.00001 unless noted). *Donepezil vs rivastigmine (one trial)* Primary: There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances and global assessment (*P* values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly fewer patients in the donepezil group withdrew from treatment after 2 years than in the rivastigmine group (OR, 0.64; 95% CI, 0.50 to 0.83; *P*=0.0006). Adverse events that occurred significantly more frequently at 12-16 weeks of treatment in the rivastigmine group than in the donepezil group included: nausea (*P*<0.00001), vomiting (*P*<0.00001), falls (*P*=0.01), hypertension (*P*=0.01), anorexia (*P*=0.0005) and weight loss (*P*=0.001), and after 16 weeks to 2 years of treatment: nausea (*P*=0.0002), vomiting (*P*<0.00001) and anorexia (*P*=0.02). No significant difference between treatment groups for serious adverse events was noted (*P* value not reported).
Tariot et al[49] Donepezil (dose varied) and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	DB, MC, PC, R Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (*P*=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared to the progressive decline seen with the donepezil-placebo treatment. The change in total mean scores favored memantine vs placebo for the CIBIC-Plus (possible score range was 1-7), 4.41 vs 4.66, respectively (*P*=0.03). Treatment discontinuations due to adverse events for memantine vs placebo were 7.4% of the patients compared to 12.4%. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Cumming et al[50] Donepezil (dose varied) and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	DB, PC, PG, PRO Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: NPI Secondary: Not reported	Primary: NPI scores significantly favored the memantine group at 12 weeks and at 24 weeks. At week 12, NPI scores increased (worsening behavior) 1.7 points in the placebo group and decreased 2.5 points in the memantine group (P<0.001). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline (P=0.002). Fewer patients developed delusions in the memantine treatment group than the placebo group (P=0.011). Secondary: Not reported
Dantoine et al[51] Rivastigmine 3 to 12 mg/day Addition of memantine 5 to 20 mg/day for non-responders of rivastigmine at end of week 16	MC, OL Patients at least 50 years of age with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6 months prior with donepezil 5 to 10 mg/day or galantamine 16 to 24 mg/day and considered not stabilized, current stabilized medications allowed	N=202 16 weeks of rivastigmine monotherapy (Phase 1) Additional 12 weeks of rivastigmine and memantine combination therapy for non-responders of rivastigmine monotherapy (Phase 2)	Primary: MMSE Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1. For those patients previously on donepezil or galantamine, responder rates were also similar (46.6 and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded more significantly than those who switched from donepezil (84.2 vs 72.3%; P=0.047). Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		Total 28 weeks		memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (*P*<0.001 and *P*<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (*P*<0.05, *P*<0.001 and *P*<0.001, respectively).
Porsteinsson et al[52] Donepezil, rivastigmine or galantamine (doses varied) and memantine 20 mg once daily vs donepezil, rivastigmine or galantamine (doses varied) and placebo	PC, R Patients with probable Alzheimer's disease, MMSE scores between 10 to 22, concurrently taking a cholinesterase inhibitor	N=433 24 weeks	Primary: ADAS-cog, CIBIC-Plus Secondary: ADCS-ADL, NPI, MMSE	Primary: No significant difference in ADAS-cog and CIBIC-Plus was found between memantine and placebo. Secondary: No significant difference in ADCS-ADL, NPI or MMSE was found between memantine and placebo.
Reisberg et al[53] Memantine 10 mg twice a day vs placebo	DB, PG Patients with moderate-to-severe Alzheimer's disease	N=252 28 weeks	Primary: CIBIC-Plus and ADCS-ADL Secondary: SIB	Primary: A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL (*P*=0.03). There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score: 4.7 placebo vs 4.4 memantine; *P*=0.03), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score: 4.8 placebo vs 4.5 memantine; *P*=0.06). Secondary: Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				period (*P*=0.002).
Winblad et al[54] Memantine 10 mg every day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C (*P*<0.016 and *P*<0.001, respectively). Separate analyses of the Alzheimer's disease population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (*P*=0.012). Secondary: No significant differences in safety were found between the groups.
Winblad et al[55] Memantine 20 mg/day vs placebo	MA Four studies: memantine as mono-therapy, 2 studies of memantine vs placebo in patients already taking an acetylcholinesterase inhibitor; patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 in subgroup with moderate-to-severe Alzheimer's disease 24 to 28 weeks	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: There was a statistically significant advantage for the memantine group over the placebo group in all 4 efficacy domains: CIBIC-Plus or global status (*P*<0.001), SIB or ADAS-Cog status (*P*<0.001), ADCS-ADL (*P*<0.001) and NPI (*P*=0.03). Secondary: Not reported
Wilkinson and Andersen[56] Memantine 20 mg/day (10 mg twice a day or	MA Patients diagnosed with moderate-to-severe Alzheimer's	N=1,826 24 to 28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
20 mg daily) vs placebo	disease		Secondary: Not reported	Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome measure (*P*<0.001). Secondary: Not reported
Ott et al[57] Continuation of memantine up to 20 mg/day vs placebo for 8 weeks then memantine 5-20 mg/day thereafter	DB, MC, OL, PG, R Patients at least 50 years of age having probable Alzheimer's disease, completed a lead-in trial that was multicenter, randomized, double-blind, placebo-controlled for 24 weeks with memantine in mild Alzheimer's disease	N=314 28 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: At least one adverse event was reported by 74.8% of patients during the 28 weeks with the most common adverse event being falls and other injuries (both 10.8%). 6.7% of patients withdrew from the study due to adverse events and the frequency was similar between the placebo-memantine group and the memantine-memantine group. Physical and lab exams were normal except for a significant increase in blood urea nitrogen levels with an incidence of 7.0% in the memantine-memantine group and 3.6% in the placebo-memantine group. Secondary: Not reported
Bakchine and Loft[58] Memantine 20 mg/day vs placebo	DB, PC Patients with mild-to-moderate Alzheimer's disease	N=470 24 weeks	Primary: ADAS-COG and CIBIC-plus Secondary: Not reported	Primary: Patients in the memantine group showed a statistically significant improvement relative to placebo in ADAS-COG and CIBIC-plus at weeks 12 and 18. There was no significant difference between the groups at week 24. Secondary: Not reported
McShane et al[59] Memantine 10 to 30 mg/day vs	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-	N=not specified Duration varied	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary:	Primary: Significant improvement at six months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (*P*=0.03); however, there was no significant difference seen for behavior and ADL scales.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	to-moderate vascular dementia		Not reported	Significant improvement at six months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (*P*<0.00001), SIB (*P*<0.00001), ADCS-ADL (*P*=0.003) and NPI (*P*=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog; *P*=0.0002, NPI; *P*=0.03). Secondary: Not reported
Maidment et al[60] Memantine 20 mg daily vs placebo or memantine 20 mg daily in combination with a cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)	MA Patients with probable Alzheimer's disease	N=1,750 Duration varied	Primary: NPI Secondary: Not reported	Primary: Compared to the placebo group patients receiving memantine improved by 1.99 on the NPI scale (95% CI, -0.08 to -3.91; *P*=0.041). Secondary: Not reported
Farlow et al[61] Donepezil 10 mg daily	DB, MC, RCT Patients 45 to 90 years of age with	N=1467 24 weeks	Primary: SIB and CIBIC Secondary:	Primary: At 24 weeks, SIB scores were significantly greater with the high dose donepezil (23 mg) than with donepezil 10 mg (2.6 vs 0.4, respectively; difference, 2.2; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs donepezil 23 mg daily	Alzheimer's disease, a MMSE score of 0 to 20 and SIB score ≤90, and Cornell Scale for Depression in Dementia score <12		Not reported	Global functioning as measured by the CIBIC plus score in the two treatment groups was comparable and the differences were nonsignificant (4.23 for 23 mg vs 4.29 for 10 mg). Donepezil 5 and 10 mg treatment showed no statistical difference in improvements. Secondary: Not reported Treatment-emergent adverse events were reported in 710 of 963 patients (73.7%) in the donepezil 23 mg and in 300 of 471 patients (63.7%) who received donepezil 10 mg. With donepezil 23 mg, mild, moderate, and severe treatment-emergent adverse events were reported in 297 (30.8%), 332 (34.5%), and 81 (8.4%) patients, respectively; with donepezil 10 mg, these proportions were 147 (31.2%), 119 (25.3%), and 34 (7.2%). The three most common severe AEs reported with the 23-mg/d dose were nausea (nine patients [0.9%] vs one [0.2%] with the 10-mg/d dose), dizziness (7 [0.7%] vs 1 [0.2%]), and vomiting (6 [0.6%] vs 0). The most commonly reported treatment-emergent adverse events considered probably related to treatment with the 23-mg/d dose were nausea (59 patients [6.1%] vs 9 [1.9%] with the 10-mg/d dose), vomiting (48 [5.0%] vs 4 [0.8%]), and diarrhea (31 [3.2%] vs 7 [1.5%]).Thirteen deaths were reported during the study or within 30 days of study discontinuation (23 mg/d, 8 patients [0.8%]; 10 mg/d, 5 patients [1.1%]); all were considered unrelated to the study medication.
Dementia				
Brodaty et al[62] Galantamine 2 to 50 mg/day, average dose 14 to 15 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe dementia	N=345 ITT N= 229 PP 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL Secondary: Not reported	Primary: For the MMSE 65% of PP patients had an increased score at the three-month assessment as compared to baseline with an overall 92% response rate. 70% of PP patients had an increased score at the six-month assessment as compared to baseline with an overall 91% response rate. 44% of ITT patients had an increased score at the six-month assessment as compared to baseline (*P* values were not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. *P* value was not reported. For CIBIC-Plus at three months, 91% of PP patients were considered responders by their physicians; 28% were unchanged, 38% were minimally improved, 22% were much improved, 4% were very much improved (*P* values not reported). For CIBIC-Plus at six months, 86% of PP patients were considered responders by their physicians; 20% were unchanged, 26% were minimally improved, 32% were much improved, 7% were very much improved. In the ITT patients, 54 % were classified as responders at six months (*P* values not reported). Most PP patients had no change in IADL scores at three and six months (*P* value not reported). Most PP patients had no change in behavior scores at three and six months (*P* value not reported). Secondary: Not reported
Auchus et al[63] Galantamine 8 to 24 mg/day; average dose 16.4±3.98 mg/day vs placebo	DB, PC, PG, R Patients meeting exact criteria for probable vascular dementia defined by National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences	N=786 26 weeks	Primary: ADAS-cog/11, ADCS-ADL Secondary: CIBIC-Plus, NPI, EXIT-25, ADAS-cog/13, ADAS-cog/10, ADAS-cog/memory	Primary: At the end of 26 weeks, a significant improvement was shown for ADAS-cog/11 with galantamine compared to placebo (–1.8 vs –0.3; *P*<0.001). No significant differences were found on ADCS-ADL between galantamine and placebo (0.7 vs 1.3; *P*=0.783). Secondary: Galantamine did not show a significant improvement vs placebo in a global clinical assessment using the CIBIC-Plus (*P*=0.069). No differences were found in NPI between the two groups, galantamine and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				End Exit-25 scores showed a favorable response for galantamine compared to placebo (*P*=0.041). ADAS-cog/13, ADAS-cog/10, and ADAS-cog/memory had a significantly higher response rate and improvement with galantamine compared to placebo (*P*<0.001, *P*<0.01 and *P*<0.05, respectively).
Mild-to-Moderate Dementia Associated with Parkinson's Disease				
Emre et al[64] Rivastigmine 3 to 12 mg/day; average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients at least 50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank and DSM-IV	N=541 Dose titration over the first 16 weeks with a subsequent assessment period of 8 weeks Total of 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR power of attention tests, D-KEFS verbal fluency test, Ten Point Clock-drawing Test	Primary: Patients who were receiving rivastigmine had significant improvement of 2.1 points in the 70-point ADAS-Cog scores vs worsening of 0.7 point in the placebo group from baseline (*P*<0.001). 19.8% of patients in the rivastigmine group and 14.5% in the placebo group clinically improved in the ADCS-CGIC scores. 13% of patients in the rivastigmine group and 23.1% in the placebo group clinically worsened in the ADCS-CGIC scores (*P*=0.007). Secondary: All secondary outcomes were significantly better in the rivastigmine group compared to placebo, as reflected by the changes in the ADCS-ADL score (*P*=0.02), NPI-10 (*P*=0.02), MMSE (*P*=0.03), CDR power of attention tests (*P*=0.009), D-KEFS verbal fluency test (*P*<0.001) and the Ten Point Clock-drawing Test (*P*=0.02).
Wesnes et al[65] Rivastigmine 3 to 12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients at least 50 years old with Parkinson's disease, according to clinical diagnostic criteria of United Kingdom Parkinson's Disease Society Brain Bank, and mild-to-moderately severe	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability Secondary: Not reported	Primary: At week 16, there was no statistical significance from baseline scores between rivastigmine and placebo for power of attention (*P*=0.11) but there was a significance at week 24 (*P*<0.01). By week 16, there was a significant improvement with continuity of attention (*P*=0.001) compared to placebo and this parameter continued to improve at week 24 (*P*=0.0001). Cognitive reaction time showed significant improvement by the end of week 24 (*P*<0.001) vs week 16 (*P*=0.064) but declined with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	dementia due to Parkinson's disease, according to DSM-IV			Reaction time variability continued to show improvement over placebo from week 16 (*P*<0.05) to week 24 (*P*<0.001). Secondary: Not reported
Maidment et al[66] Rivastigmine (3 to 12 mg/day) vs placebo	MA Patients diagnosed with mild-to-moderately severe dementia, which developed at least 2 years after Parkinson's disease was diagnosed	N=541 (1 study) 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: MMSE, ADCS-ADL, NPI, CDR, D-KEFS, Ten Point Clock-drawing Test, UPDRS, adverse events	Primary: Significant improvement in ADAS-Cog was found for patients treated with rivastigmine over placebo (WMD, –2.80; 95% CI, –4.26 to –1.34; *P*=0.0002). Results in ADCS-CGIC significantly favored patients treated with rivastigmine over placebo (WMD, –0.50; 95% CI, –0.77 to –0.23; *P*=0.0004). 19.8% of rivastigmine patients experienced "clinically meaningful (moderate or marked) improvement" compared to 14.5% of the placebo group; 13.0% of rivastigmine patients experienced "clinically meaningful worsening" compared to 23.1% in the placebo group (*P* values not reported). Secondary: Results for MMSE significantly favored patients treated with rivastigmine over placebo (WMD, 1.00; 95% CI, 0.33 to 1.67; *P*=0.003). Results for ADCS-ADL significantly favored patients treated with rivastigmine over placebo (WMD, 2.50; 95% CI, 0.43 to 4.57; *P*=0.02). Results for NPI significantly favored patients treated with rivastigmine over placebo (WMD, –2.00; 95% CI, –3.91 to –0.09; *P*=0.04). For CDR no statistically significant difference was found (*P*=0.25). For D-KEFS, results significantly favored patients treated with rivastigmine over placebo (WMD, 2.80; 95% CI, 1.47 to 4.13; *P*<0.0001). Full UPDRS was not reported. No statistically significant difference was found for motor score, including tremor (*P*=0.83 and *P*=0.84).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly more patients in the rivastigmine group than the placebo group experienced one or more adverse events (*P*=0.0006). Adverse events included: nausea, vomiting, tremor, and dizziness. Significantly more patients treated with rivastigmine withdrew from treatment for any reason than those treated with placebo (*P*=0.02).

*Product not available in the United States.
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double dummy, ER=extended release, IR=immediate release, MA=meta analysis, MC=multicenter, OC=observational case, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, WMD=weighted mean difference
Miscellaneous abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale, ADAS-cog/10=10-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/11=11-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/13=13-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/memory=Alzheimer's Disease Assessment Scale-Cognitive/Memory, ADAS-noncog=Alzheimer Disease Assessment Scale-Noncognitive, ADCPQ=Alzheimer's Disease Caregiver Preference Questionnaire, ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, ADCS-ADL-sev=Alzheimer Disease Cooperative Study-Activities of Daily Living-severe version, ADCS-CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, ADL=Activity of Daily Living, BADLS=Bristol Activities of Daily Living Scale, BEHAV-AD= Behavioral Pathology in Alzheimer's Disease Rating Scale, BGP=Behavioral Rating Scale for Geriatric Patients, BrADL=Bristol Activities of Daily Living Scale, CBQ=Caregiver Burden, Questionnaire, CDR=Cognitive Drug Research, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression of Improvement scale, CIBIC=Clinician Interview-Based Impression of Change Scale, CIBIC-Plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input, DAD=Disability Assessment, D-KEFS=Delis-Kaplan Executive Function System, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EXIT-25=Executive Interview, FAST=Functional Assessment Staging, GBS=Gottfries-Bråne-Steen scale, GDS=Global Deterioration Scale, IADL=Instrumental Activity of Daily Living, ITT=intent-to-treat, LOCF=last observed case forward, MMSE=Mini-Mental Status Exam, NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, NPI=Neuropsychiatric Inventory, NPI-10=10-item Neuropsychiatric Inventory, PRC=prolonged-release capsule, PDS=Progressive Deterioration Scale, PP=per-protocol, RUSP=Resource Utilization for Severe Alzheimer Disease Patients, SIB=Severe Impairment Battery, UPDRS=Unified Parkinson's Disease Rating Scale

Special Populations

Table 5. Special Populations[5-9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Donepezil	No dosage adjustment required in elderly. Safety and efficacy not established in the pediatric population.	No dosage adjustment reported.	No dosage adjustment reported.	C	Unknown
Galantamine	No dosage adjustment required in elderly. Safety and efficacy not established in the pediatric population.	Not recommended in severe impairment and dose titration should be done with caution in moderate impairment.	Not recommended in severe impairment and dose titration should be done with caution in moderate impairment.	B	Unknown
Memantine	Pharmacokinetics in younger and elderly patients are similar. Safety and efficacy not established in the pediatric population.	Renal dose adjustment required in patients with severe renal dysfunction.	Administer with caution in patients with severe hepatic dysfunction.	B	Unknown
Rivastigmine	No dosage adjustment required in elderly. Safety and efficacy not established in the pediatric population.	Since dose is titrated to need, no dosage adjustment necessary.	Since dose is titrated to need, no dosage adjustment necessary.	B	Unknown

Adverse Drug Events

Discontinuations due to adverse events for rivastigmine, donepezil, and galantamine are low and similar to placebo. Gastrointestinal adverse events occur most frequently among the cholinesterase inhibitor agents. Donepezil frequently results in lower gastrointestinal adverse events compared to the other agents. Additive risk of adverse events may be expected with coadministration of these drugs, or with inadequate washout periods between agents. One report of fatal aspiration pneumonia has been published after initiation of rivastigmine and discontinuation of donepezil with no washout period between therapies.[58] A washout period should be considered, and is usually recommended when switching between cholinesterase inhibitors. The most common adverse drug events reported with cholinesterase Inhibitors are noted in Table 6.

Adverse events reported with were memantine are minimal and include dizziness, headache, confusion, constipation, and cough. Other adverse events reported include agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia and arthralgia.[6]

Table 6. Adverse Drug Events[5-10] (%)

Adverse Event	Donepezil	Galantamine	Memantine	Rivastigmine (oral)	Rivastigmine (transdermal)
Cardiovascular					
Angina pectoris	-	-	-	≥1	-
Atrial fibrillation	≥1	-	-	≥1	-
Bradycardia	≥1	2	-	≥1	-
Chest pain	1 to 2	≥1	-	≥1	-
Electrocardiogram abnormal	≥1	-	-	-	-
Heart failure	≥1	-	-	≥1	-
Hemorrhage	2	-	-	-	-
Hot flashes	≥1	-	-	≥1	-
Hypertension	1-3	-	4	3	-
Hypotension	≥1	-	-	≥1	-
Myocardial infarction	-	-	-	≥1	-
Palpitation	-	-	-	≥1	-
Postural hypotension	-	-	-	≥1	-
Syncope	2	2	-	3	-
Vasodilation	≥1	-	-	-	-
Central Nervous System					
Abnormal crying	≥1	-	-	-	-
Abnormal dreams	3	-	-	-	-
Abnormal thinking	-	-	-	-	-
Aggression	≥1	-	-	3	-
Agitation	≥1	-	-	≥1*	12 to 14
Anxiety	-	-	-	-	1 to 5
Aphasia	≥1	-	-	-	-
Bradykinesia	-	-	-	≥1*	-
Confusion	2	-	6	1 to 8	-
Convulsion	≥1	-	-	≥1	-
Delusions	≥1	-	-	-	-
Depression	2 to 3	7	-	1-6	2 to 5
Dizziness	2 to 8	9	7	6 to 21	1 to 7
Dyskinesia	-	-	-	≥1*	-
Emotional lability	2	-	-	-	-
Fatigue	2†, 5	5	2	4 to 9	1 to 4
Gait abnormality	≥1	-	-	≥1	-
Hallucination	3	-	3	4	2 to 5
Headache	4 to 10	8	6	17	1 to 4
Hostility	3	-	-	-	-
Hyperkinesia	-	-	-	-	-
Insomnia	3†, 5 to 9	5	-	3 to 9	1 to 7
Irritability	≥1	-	-	-	-
Libido increased	≥1	-	-	-	-
Malaise	-	≥1	-	5	-
Nervousness	1-3	-	-	-	-
Paranoid reaction	-	-	-	≥1	-
Paresthesia	≥1	-	-	≥1	-
Parkinson's disease	-	-	-	3*	-

worsening					
Parkinsonism	-	-	-	2*	-
Personality disorder	2	-	-	-	-
Restlessness	≥1	-	-	≥1*	-
Somnolence	2	4	3	4 to 5	-
Transient ischemic attack	-	-	-	≥1*	-
Tremor	≥1	3	-	4 to 10	≥1
Vertigo	≥1	-	-	≥1*	1 to 2
Wandering	≥1	-	-	-	-
Dermatological					
Diaphoresis	≥1	-	-	-	-
Eczema	3	-	-	-	-
Erythema	-	-	-	-	12 to 13
Facial/skin flushing	-	-	-	-	-
Pruritis	≥1	-	-	-	≥1
Rash	≥1	-	-	≥1	-
Skin ulcer	≥1	-	-	-	-
Urticaria	≥1	-	-	-	-
Endocrine and Metabolic					
Dehydration	1 to 2	-	-	1 to 2	≥1
Edema	≥1	-	-	≥1	-
Hyperlipemia	2	-	-	-	-
Peripheral edema	≥1	-	-	-	-
Weight decrease	1 to 3, 5†	5 to 7	-	3	1 to 8
Gastrointestinal					
Abdominal pain	≥1	5	-	4 to 13	1 to 4
Anorexia	4 to 8	7 to 9	-	6 to 17	2 to 9
Bloating	≥1	-	-	-	-
Constipation	≥1	-	5	5	≥1
Diarrhea	8†, 10	6 to 12	-	7 to 19	1 to 10
Dyspepsia	≥1	5	-	1 to 9	-
Epigastric pain	≥1	-	-	-	-
Fecal incontinence	≥1	-	-	≥1	-
Flatulence	-	≥1	-	4	-
Gastritis	-	-	-	≥1	≥1
Gastroenteritis	≥1	-	-	-	-
Gastrointestinal bleeding	≥1	-	-	-	-
Nausea	6 to 11, 12†	13 to 24	-	29 to 47	4 to 23
Nausea/vomiting	-	-	-	-	-
Vomiting	5 to 8, 9†	6 to 13	3	17 to 31	2 to 19
Genitourinary					
Cystitis	≥1	-	-	-	-
Frequent urination	2	-	-	-	-
Hematuria	≥1	3	-	≥1	-
Urinary incontinence	2 to 3	≥1	-	-	≥1
Urinary tract infection	≥1	8	-	7	2 to 10
Hematologic					
Anemia	≥1	3	-	≥1	≥1

Ecchymosis	4 to 5	-	-	-	-
Epistaxis	-	-	-	≥1	-
Purpura	-	-	-	-	-
Lab Test Abnormalities					
Elevated alkaline phosphatase	≥1	-	-	-	-
Elevated creatinine	3	-	-	-	-
Elevated LDH	≥1	-	-	-	-
Elevated transaminase	-	-	-	-	-
Musculoskeletal					
Arthralgia	-	-	-	-	-
Arthritis	1 to 2	-	-	≥1	-
Asthenia	≥1, 2†	≥1	-	2 to 6	1 to 6
Ataxia	≥1	-	-	≥1	-
Back pain	3	-	-	≥1	-
Bone fracture	≥1	-	-	-	-
Leg cramps	-	-	-	≥1	-
Muscle cramps	6	-	-	-	-
Myalgia	-	-	-	≥1	-
Ocular					
Blurred vision	≥1	-	-	-	-
Cataract	≥1	-	-	≥1	-
Conjunctivitis	-	-	-	-	-
Eye irritation	≥1	-	-	-	-
Respiratory					
Bronchitis	≥1	-	-	-	-
Cough increased	≥1	-	4	-	-
Dyspnea	≥1	-	2	≥1	-
Pharyngitis	≥1	-	-	-	-
Pneumonia	≥1	-	-	-	≥1
Rhinitis	-	4	-	4	-
Sinusitis	-	-	-	-	-
Upper respiratory tract infection	-	-	-	-	-
Other					
Accident	7 to 13	-	-	-	-
Accidental trauma	-	-	-	1 to 10	-
Allergy	-	-	-	≥1	-
Chills	-	-	-	-	-
Fall	-	-	-	-	3 to 8
Fever	2	≥1	-	≥1	-
Flu syndrome	≥1	-	-	3	-
Infection	1 to 11	-	-	-	-
Influenza	≥1	-	-	-	-
Pain	3 to 9	-	3	-	-
Tinnitus	-	-	-	≥1	-

✔ =Percent not specified.
- Event not reported.
LDH=lactic dehydrogenase.
*Reported only in trials for Parkinson's disease–associated dementia.
†23 mg tablet strength.

Contraindications/Precautions

Cholinesterase inhibitor use is contraindicated in patients with hypersensitivity to the cholinesterase inhibitor or to any excipients used in the formulation.

Cholinesterase inhibitors should be used with caution in patients with asthma, chronic obstructive pulmonary disease, sick sinus syndrome or other supraventricular cardiac conditions. In addition, due to the mechanism of action of the cholinesterase inhibitors, gastric acid secretion may be increased as a result of increased cholinergic activity. Therefore, special caution should be used in patients at increased risk of developing ulcers or those with a history of peptic ulcer disease.[5-9]

Memantine use is contraindicated in patients with hypersensitivity to the N-methyl-D-aspartate (NMDA) receptor antagonist or to any excipients used in the formulation. Caution should be taken in patients taking memantine with neurological or genitourinary conditions as memantine has not been evaluated in patients with seizure disorders and an increase in urine pH may decrease the urinary elimination resulting in increased memantine levels.[6]

Drug Interactions

Rivastigmine is metabolized by esterases rather than CYP enzymes theoretically resulting in no drug interactions with drugs metabolized by the following isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8 or CYP2C19.[68] Galantamine does not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. Potential changes in serum levels of galantamine exist when coadministered with fluoxetine, cimetidine, ketoconazole, erythromycin, paroxetine and other medications that inhibit or induce CYP2D6 and CYP3A4.[5-9]

There are no significant drug interactions listed for the NMDA receptor antagonist, memantine.[6]

Dosage and Administration

Donepezil and galantamine extended release capsules are the only oral agents approved for once daily dosing. Galantamine and rivastigmine are available in a liquid dosage form and donepezil is available as an orally disintegrating tablet. Rivastigmine is also available in a once daily transdermal patch. Memantine is available in a solution and tablet, taken twice daily. Although studies indicate the clearance of donepezil and rivastigmine may be altered in renal and hepatic impairment, neither manufacturer has provided specific recommendations for dosing in patients with renal or hepatic disease. Galantamine use is not recommended in patients with severe hepatic or renal impairment, and caution should be used when the drug is given to patients with moderate hepatic or renal disease. When given with food, the gastrointestinal tolerability of the cholinesterase inhibitors may be improved.[5-9] The usual dosing regimens for the Alzheimer agents are summarized in Table 7.

Table 7. Dosing and Administration[5-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Donepezil	Mild to moderate Alzheimer's disease: Tablet and orally disintegrating tablet: Initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; maintenance, 5 to 10 mg daily Moderate to severe Alzheimer's disease: Tablet: Initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; may increase to 23 mg	Safety and efficacy not established in the pediatric population.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	daily after three months on 10 mg daily dose Orally disintegrating tablet: Initial, 5 mg daily; may increase to 10 mg daily after four to six weeks		
Galantamine	Mild to moderate Alzheimer's disease dementia: Extended-release capsule: Initial, 8 mg daily; maintenance, 16 to 24 mg daily Tablet and oral solution: Initial, 4 mg twice a day with the morning and evening meals; maintenance: 8 to 16 mg twice a daily	Safety and efficacy not established in the pediatric population.	Extended-release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg
Memantine	Moderate to severe Alzheimer's disease: Solution and tablet: Initial, 5 mg once daily, increase dose by 5 mg at weekly intervals (twice daily dosing); maintenance, 10 mg twice daily	Safety and efficacy not established in the pediatric population.	Solution: 10 mg/5 mL Tablet: 5 mg 10 mg 4 week titration pack
Rivastigmine	Mild to moderate Alzheimer's disease dementia: Capsule and solution: Initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: Initial, 4.6 mg/24 hours; maintenance, 9.5 mg/24 hours or 13.36 mg/24 hours Severe Alzheimer's disease dementia: Transdermal patch: Initial, 4.6 mg/24 hours; maintenance, 13.36 mg/24 hours Mild to moderate Parkinson's disease dementia: Capsule and solution: Initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch:	Safety and efficacy not established in the pediatric population.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours

Generic Name	Adult Dose	Pediatric Dose	Availability
	Initial, 4.6 mg/24 hours; maintenance, 9.5 mg/24 hours or 13.36 mg/24 hours		

Clinical Guidelines

Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in Alzheimer's disease (AD). It is believed that the memory loss in AD is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is Food and Drug Administration (FDA) approved only for moderate-severe dementia and the cholinesterase inhibitors are indicated for mild-to-moderate disease with the exception of donepezil and rivastigmine which also is indicated for moderate-to-severe disease. Rivastigmine has the additional indication of dementia associated with Parkinson's disease.[64-65]

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Neurology: **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2003)**[68]	Pharmacologic treatment of Alzheimer's disease (AD) • Cholinesterase inhibitors should be considered in patients with mild-to-moderate AD, although studies suggest a small average degree of benefit. • Vitamin E (1,000 IU by mouth twice a day) should be considered in an attempt to slow progression of AD. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatory or other putative disease-modifying agents specifically to treat AD because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat AD. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. Pharmacologic treatment for noncognitive symptoms of dementia • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents may be better tolerated compared to traditional antipsychotics. • Selected antidepressants (eg, selective serotonin-reuptake inhibitors and tricyclics) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. Educational Interventions for patients with dementia and/or caregivers • Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with AD to delay time to nursing home placement. • Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary antipsychotics. • As part of this practice guideline, additional interventions other than education for patients and caregivers are available for functional

Clinical Guideline	Recommendation(s)
	behaviors, problem behaviors, and care environment alterations.
American Academy of Neurology: **Practice Parameter: Diagnosis of Dementia: An Evidence-Based Review (2004)**[70]	Management of dementia • Cognitive symptoms of AD are treated with cholinesterase inhibitors and vitamin E. • Cholinesterase inhibitors have been proven effective in patients with mild-to-moderate AD and vitamin E may be considered to slow progression of AD. • Agitation, depression and psychosis should be treated initially with environmental manipulation. If this is not effective, then antipsychotics may be used. Tricyclics, monoamine oxidase inhibitors, and selective serotonin-reuptake inhibitors should be considered to treat depression. • Caregiver participation in educational programs and support groups is recommended.
British Association for Psychopharmacology: **Clinical Practice with Anti-dementia Drugs: A Consensus Statement (2006)**[69]	• Cholinesterase inhibitors are effective in the treatment of mild-to-moderate AD. • One cholinesterase inhibitor should be switched to another if the first is not tolerated or effective. • Memantine is effective in the treatment of moderate-to-severe AD. • Memantine may be added to a cholinesterase inhibitor. • Cholinesterase inhibitors may be used for the treatment of both dementia with Lewy bodies and Parkinson's disease dementia, including neuropsychiatric symptoms. • Cholinesterase inhibitors and memantine may be used for the treatment of cognitive impairment in vascular dementia, though effect sizes are small and may not be clinically significant. • No distinction is made between cholinesterase inhibitors in terms of efficacy.

Conclusions

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease (AD).

All cholinesterase inhibitors have the Food and Drug Administration (FDA)-approved indication for mild-to-moderate Alzheimer's disease (AD) while donepezil has the added indication for moderate-to-severe AD and rivastigmine for severe AD. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has Food and Drug Administration approval for moderate-to-severe dementia of AD.

Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients. However, a review by Liepelt et al describes efficacy from donepezil similar to that of rivastigmine.[76] The Quality Standards Subcommittee of the American Academy of Neurology also reported comparable efficacy between rivastigmine and donepezil.[73]

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate AD. Use of donepezil, galantamine or rivastigmine in the treatment of cognitive and neuropsychiatric complications of Alzheimer's disease provides comparable outcomes. Memantine is supported in one guideline for moderate-severe AD. In addition Memantine has also been studied as add-on therapy with donepezil and galantamine with results suggesting better tolerability than monotherapy. Although the addition of memantine to any current cholinesterase regimen may confer additional benefit, particularly in the area of tolerability and caregiver burden the overall clinical impact of these agents are marginal.[72]

Currently there are limited head-to-head trials comparing the efficacy of the cholinesterase inhibitors and no data comparing memantine to other agents used to treat AD. Better designed head-to-head studies are needed between these agents to fully evaluate their comparative efficacy. Efficacy data on cognitive function from trials comparing the cholinesterase inhibitors have shown that the cholinesterase inhibitors are equally effective. The British Association for Psychopharmacology has determined that all cholinesterase inhibitors have shown equal efficacy and differ only in frequency of side effects.[70]

There is insufficient clinical evidence to conclude that one agent is safer or more efficacious than another.

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