Therapeutic Class Overview
Alzheimer's Agents

Therapeutic Class

- **Overview/Summary:** Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[1] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately eight to 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

  The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

  There are four agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an NMDA receptor antagonist (memantine).[4-12] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate.

  In February of 2014, Forest Laboratories notified the prescriber community that they plan to discontinue the sale of Namenda® tablets on August 15, 2014. They also note that they will continue to sell the Namenda® oral solution and Namenda XR® extended release capsules.[13]

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Parasympathomimetic (Cholinergic Agents)			
Donepezil (Aricept®*, Aricept ODT®*)	Mild-to-moderate dementia of the Alzheimer's type Moderate-to-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®*)	Mild-to-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	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		12 mg	
Rivastigmine (Exelon®*, Exelon Patch®)	Mild-to-moderate dementia of the Alzheimer's type (capsule and solution) Mild, moderate, and severe dementia of the Alzheimer's type (transdermal patch) Mild-to-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	✔
Central Nervous System Agents, Miscellaneous			
Memantine (Namenda®, Namenda XR®)	Moderate-to-severe dementia of the Alzheimer's type	Extended release capsule: 7 mg 14 mg 21 mg 28 mg Solution: 10 mg/5 mL Tablet: 5 mg 10 mg	-

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

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the Alzheimer's agents.[14-103]
- Overall there is limited head to head data available comparing the efficacy of the different agents used to treat Alzheimer's disease. Several different outcomes have been assessed using more than forty different instruments, including cognition, global function, behavior and quality of life. There is inconsistent evidence from well-designed trials that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. These findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of well-designed clinical trials were less than one year. There are very few studies that directly compare their various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to directly compare the results.
- The newest agent in the class, memantine extended-release has been shown to be efficacious when compared to placebo.[52]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[104-108]
    - Supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease.
    - Memantine is effective in the treatment of moderate-to-severe Alzheimer's disease.

  - Memantine may be added to a cholinesterase inhibitor.
- Other Key Facts:
  - Currently donepezil, galantamine and the oral formulation of rivastigmine are available generically.
  - Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients.
  - Forest Laboratories notified the prescriber community that they plan to discontinue the sale of Namenda® tablets on August 15, 2014. They also note that they will continue to sell the Namenda® oral solution and Namenda XR® extended release capsules.[13]

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Therapeutic Class Review
Alzheimer's Agents

Overview/Summary

Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[1] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately eight to 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

There are four agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an NMDA receptor antagonist (memantine).[4-12] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate.

In February of 2014, Forest Laboratories notified the prescriber community that they plan to discontinue the sale of Namenda® tablets on August 15, 2014. They also note that they will continue to sell the Namenda® oral solution and Namenda XR® extended release capsules.[13]

Medications

Table 1. Medications Included Within Class Review

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

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

Indications

Table 2. Food and Drug Administration Approved Indications[4-12]

Indication	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Mild-to-moderate dementia of the	✔	✔	✔ †	

Indication	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Alzheimer's type				
Mild, moderate, and severe dementia of the Alzheimer's type			✔ ‡	
Moderate-to-severe dementia of the Alzheimer's type	✔			✔
Mild-to-moderate dementia associated with Parkinson's disease			✔	

*Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease.
†Capsule and solution.
‡Transdermal patch.

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

Table 3. Pharmacokinetics[4-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Parasympathomimetic (Cholinergic Agents)					
Donepezil	Percent not reported	96	Liver	Renal (57) Feces (15)	70
Galantamine	90	18	Liver	Renal (95) Feces (5)	7
Rivastigmine	Oral: 36	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.5 Transdermal: 3.0
Central Nervous System Agents, Miscellaneous					
Memantine	Well absorbed	45	Liver, partial	Renal (48)	60 to 80

Clinical Trials

Clinical trials have demonstrated the safety and efficacy of the Alzheimer's agents.[14-103] Overall there is limited head to head data available comparing the efficacy of the different agents used to treat Alzheimer's disease. There is inconsistent evidence from well-designed trials that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. There are very few studies that directly compare their various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to directly compare the results.

The newest agent in the class, memantine extended-release has been shown to be efficacious when compared to placebo.[52]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alzheimer's Disease				
Geldmacher et al.[14] (2003) Donepezil 5 mg/day	OS Patients with Alzheimer's disease	N=1,115 Variable duration	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 nine 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
Burns et al.[15] (2007) Donepezil 5 to 10 mg/day	MC, OL Patients ≥50 years of age with mild-to-moderate Alzheimer's disease	N=579 132 weeks	Primary: ADAS-cog, CDR-SB, IDDD, QoLS, and adverse events Secondary: Not reported	Primary: Mean changes in ADAS-cog scores of all patients were improved by approximately two points after six weeks (cumulative week 36) and one point after 12 weeks (cumulative week 42), with improvement compared to the start of OL treatment. At week 24 (cumulative week 54), mean ADAS-cog scores still showed improvement (approximately 0.5 points) compared to those scores reported at the start of OL treatment. From 24 weeks, ADAS-cog scores declined over the remainder of the study. At the end of 132 weeks of OL treatment (162 weeks total follow-up), the change from DB baseline was 15.6 points for all patients. No difference was seen between patients who had previously received placebo in the DB phase vs those receiving donepezil for the entire treatment period. CDR-SB scores improved slightly over the first 12 weeks (up to cumulative week 42) of OL treatment and then slowly declined for the remainder of the study period (up to cumulative week 162). Mean IDDD total scores were maintained over the first 24 weeks of OL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment to within approximately 1 point relative to those at the beginning of this study period. Mean IDDD scores were 138.1 at week 0, 136.9 at week 12, 138.9 at week 24 and 170.8 at week 132 (162 weeks of total follow-up). At the start of the OL extension, QoLS scores were improved compared to baseline, with a mean change of 3.03. The scores remained above the baseline level at weeks six and 12 of OL treatment. At the end of 132 weeks of OL treatment, the decline from the baseline for the DB study was -46.2. Overall, 85% of patients experienced at least one treatment-emergent adverse event. The most common adverse events included diarrhea (12%), nausea (11%), infection (11%) and accidental injury (10%). Nonfatal all-causality and treatment-related serious adverse events were reported for 25 and 7% of patients, respectively. Seventeen patients died during the study or within four weeks after discontinuation of donepezil. The most common causes of death were pneumonia (seven patients) and cerebrovascular accident (two patients). Fifteen deaths were considered unrelated to donepezil. Two deaths, one due to a cerebral hemorrhage diagnosed on day five of treatment and another due to a suspected myocardial infarction on day 55, were considered by the investigators to be possibly related to donepezil. Secondary: Not reported
Hashimoto et al.[16] (2009) Donepezil 5 mg/day	OS, PRO Patients with Alzheimer's disease	N=416 12 weeks	Primary: MMSE Secondary: Not reported	Primary: There were significant changes in mean scores on the MMSE (0.9; P<0.01) from baseline to week 12. There was a significant decrease in the personal strain score at week 12 (P=0.002). There was no significant improvement was in role strain. There was no significant decrease in the time spent supervising Alzheimer's disease patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Homma et al.[17] (2009) Donepezil 10 mg/day	OL Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12	N=189 52 weeks	Primary: SIB, and BEHAVE-AD Secondary: Not reported	Primary: The mean change in SIB scores during the OL study showed improvement until week 24, followed by a decline by week 36. For those patients receiving 52 weeks of treatment, the mean change in SIB from baseline (enrollment in OL study) was –6.1. The mean change in SIB declined more rapidly after 24 weeks. For the BEHAVE-AD, little change was observed during the OL study. The change from baseline to week 24 and week 52 was 0.7 and 0.5, respectively. The level of behavioral symptoms in the study population was low. Overall, 177 patients (93.7%) experienced at least one adverse event. Severe adverse events were reported by 15 patients (7.9%) and serious adverse events were reported by 33 patients (17.5%). The most common adverse events were nasopharyngitis, diarrhea, nausea and vomiting. Secondary: Not reported
Courtney et al.[18] (2004) Donepezil 5 to 10 mg/day vs placebo	DB, RCT Patients with Alzheimer's disease	N=565 156 weeks	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 (95% CI, 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 RR 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 RR of progression of disability or entering institutional care was 0.96 (95% CI, 0.74 to 1.24; P=0.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Similarly, 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: Not reported
Sabbagh et al.[19] (2013) Donepezil 23 or 10 mg/day	Post hoc of a 24-week, DB, RCT Patients with moderate to severe Alzheimer's disease (baseline MMSE 0 to 20)	N= Duration not specified	Primary: Cognitive changes in subgroups of patients based on selected baseline and demographic characteristics Secondary: Not reported	Primary: Donepezil 23 mg/day provided statistically significant incremental cognitive benefits over donepezil 10 mg/day irrespective of baseline functional severity, measured by scores on the ADCS-ADL -severe version (P<0.05). When patients were categorized by baseline cognitive severity (MMSE score), significant benefits of donepezil 23 mg/day over 10 mg/day were seen in both subgroups when based on MMSE scores of 0 to 9 vs 10 to 20 (P<0.02 and P<0.01, respectively), and in the more severe subgroup when based on MMSE scores of 0 to 16 vs 17 to 20 (P<0.0001 and P>0.05). Statistically significant incremental cognitive benefits of donepezil 23 mg/day over 10 mg/day were also observed regardless of age, gender, weight, or prestudy donepezil 10mg/day treatment duration (P<0.05). In the multivariate analysis, the only significant interaction was between treatment and baseline MMSE score. Secondary: Not reported
Tariot et al.[20] (2012) Donepezil 23 mg/day	OL Patients with Alzheimer's disease	N=915 12 months	Primary: Safety analyses comprised examination of the incidence, severity, and timing of treatment-emergent	Primary: In total, 674 patients (74.7%) reported at least one adverse event; in 320 of these patients (47.5%) at least one adverse event was considered to be possibly or probably study drug related. The majority of patients reporting adverse events (81.9%) had adverse events of mild or moderate severity. There were 268 patients (29.7%) who discontinued early, of which 123 (13.6%) were due to adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events; changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to adverse events all at months three, six, nine, and 12 Secondary: Not reported	Patients who had increased donepezil dose from 10 mg/day to 23 mg/day had slightly higher rates of adverse events than patients who were already receiving 23 mg (78.0 and 16.9 vs 72.8 and 14.0%, respectively). The incidence of new adverse events declined rapidly after the first two weeks and remained low throughout the duration of the study. Secondary: Not reported
Winblad et al.[21] (2006) RCT Donepezil 10 mg/day vs placebo OL Donepezil 5 mg daily for 28 days, then 10 mg/day per clinician's judgment	DB, OL, PC Patients 40 to 90 years of age with a probable or possible diagnosis of Alzheimer's disease	N=286 52-week RCT with a 2-year OL extension phase	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rogers et al.[22] (1998) Donepezil 5 mg/day vs donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients with mild-to-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
Winblad et al.[23] (2006) Donepezil 10 mg/day vs placebo	DB, PC, PG Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 10 and a FAST rating of stage 5 to 7c)	N=248 6 months	Primary: SIB Secondary: MMSE, NPI, and CGI-I	Primary: At six months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo for SIB (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).
Black et al.[24] (2007) Donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 12, modified Hachinski Ischemic	N=343 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	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 declined from baseline, and the treatment difference was NS (P=0.3574).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	score ≤6, and FAST score ≥6)			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. The RUSP scores also had low average responses with little movement from baseline and no significant differences.
Homma et al.[25] (2008) Donepezil 5 to 10 mg/day vs placebo	DB, MC, PC, RCT Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12 and diagnosis confirmed by neuroimaging)	N=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev and BEHAVE-AD	Primary: Donepezil 5 and 10 mg/day were more effective than placebo on the SIB. At week 24, patients in the donepezil 5 mg/day group had a significant change from baseline of 2.5 points and those in the donepezil 10 mg/day group had a significant change from baseline of 4.7 points. Patients in the placebo group showed significant worsening (–4.2 points) during the course of the study (P<0.001 vs placebo). For the CIBIC-Plus, the analysis was performed on the seven categories of change as well as the three collapsed categories of improved, no change and worsened. In the seven-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.003); however, there was no difference with 5 mg/day (P=0.151). In the collapsed-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.001); however, there was no difference with 5 mg/day (P=0.129). Secondary: For the ADCS-ADL-sev, there was no significant differences between donepezil and placebo (placebo group, –1.1 points; donepezil 5 mg/day group, –0.1 points; donepezil 10 mg/day group, –0.3 points). For the BEHAVE-AD, there was no significant differences between donepezil and placebo (placebo group, –0.5; donepezil 5 mg/day group, –

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.5; donepezil 10 mg/ day group, –0.1). Treatment-emergent adverse events were reported by 73.3% of placebo patients, 78.2% of donepezil 5 mg/day patients and 83.3% of donepezil 10 mg/day patients. There was no significant difference in adverse events between the donepezil groups and the placebo group. The most common adverse events reported are consistent with the known cholinergic side effects of donepezil. Serious adverse events were reported by 15 placebo patients (14.3%), 12 donepezil 5 mg/day patients (11.9%) and 10 donepezil 10 mg/day patients (10.4%). Five patients died during the treatment period. The causes of death were acute pneumonia (placebo group), acute myocardial infarction (donepezil 5 mg/day group), suspected stomach cancer (donepezil 5 mg/day group; the patient died 80 days after discontinuation), vomit-induced tracheal occlusion (donepezil 10 mg/day group; the patient died seven days after completion) and arrhythmia (donepezil 10 mg/day group).
Birks et al.[26] (2006) Donepezil 5 to 10 mg/day vs placebo	MA Patients with Alzheimer's disease	N=5,796 (24 trials) 12 to 60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: A 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). A 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 in 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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
Wallin et al.[27] (2007) Donepezil 5 to 10 mg/day vs historical data	MC, PRO Patients ≥40 years of age with probable Alzheimer's disease	N=435 3 years	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE, patients had a mean score of 22.0 at baseline and 19.1 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, patients had a mean score of 20.7 at baseline and 26.1 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 to 9 points in 12 months without treatment. Scores for the treatment group were significantly better than predicted scores for non-treatment (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 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 six months was 1.01, at 12 months 2.19, and at 36 months 6.18. Secondary: Not reported
Farlow et al.[28] (2010) Donepezil 10 mg/day	DB, MC, RCT Patients 45 to 90 years of age with moderate-to-severe	N=1,467 24 weeks	Primary: Efficacy as measured by SIB-cognition and CIBIC-	Primary: After 24 weeks, the change in SIB-cognition score was significantly greater with donepezil 23 mg/day compared to donepezil 10 mg/day (2.6 vs 0.4, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs donepezil 23 mg/day	Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks		global function rating; tolerability Secondary: Not reported	There was no significant different in CIBIC score with donepezil 23 mg/day compared to donepezil 10 mg/day (4.23 vs 4.29, respectively). In a post-hoc analysis, the least square mean changes in SIB score and CIBIC treatment effect at end point were greater with donepezil 23 mg/day compared to donepezil 10 mg/day in patients with more advanced Alzheimer's disease compared to less impaired patients (SIB, 1.6 vs -1.5, respectively; P<0.001; CIBIC, 4.31 vs 4.42; P=0.028). Treatment emergent adverse events were reported in 73.7% of patients who received donepezil 23 mg/day and in 63.7% of patients who received donepezil 10 mg/day. Adverse events were reported as follows with donepezil 23 mg/day: mild (30.8%), moderate (34.5%), and severe (8.4%). The most common treatment emergent adverse events were nausea (6.1%), vomiting (5%) and diarrhea (3.2%). Severe treatment emergent adverse events that were reported included nausea (0.9%), dizziness (0.7%) and vomiting (0.6%). Adverse events were reported as follows with donepezil 10 mg/day: mild (31.2%), moderate (25.3%), and severe (7.2%). The most common treatment emergent adverse events were nausea (1.9%), vomiting (0.8%) and diarrhea (1.5%). Severe treatment emergent adverse events that were reported included nausea (0.2%) and dizziness (0.2%). Secondary: Not reported
Ferris et al.[29] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12	N=1,467 24 weeks	Primary: SIB-Language scale and 21-item SIB-derived language scale Secondary: Correlation of SIB-Language	Primary: At week 24, there was an improvement in language noted with donepezil 23 mg/day compared to a decline in language function with donepezil 10 mg/day (SIB-Language scale treatment difference, 0.8; P=0.0013, SIB-derived language scale treatment difference, 0.8; P=0.0009). Secondary: At week 24, SIB-Language scale and SIB-derived language scale scores were moderately correlated with scores on the ADCS-ADL-sev and CIBIC-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	weeks		scale and SIB-derived language scale with ADCS-ADL-sev, CIBIC-plus/CIBIC-plus, and MMSE	plus. Results were similar in both moderate (MMSE, 17 to 20) and severe (MMSE, 0 to 16) Alzheimer's disease patients.
Farlow et al.[30] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,434 24 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: Of the 963 patients receiving donepezil 23 mg/day and 471 patients receiving donepezil 10 mg/day, a total of 71.1 and 84.7% completed the study, respectively. The most common adverse events causing early discontinuation were higher in the donepezil 23 mg/day group compared to the donepezil 10 mg/day group (18.6 vs 7.9%, respectively). Adverse events that contributed the most to the discontinuations were vomiting (2.9 vs 0.4%, respectively), nausea (1.9 vs 0.4%, respectively), diarrhea (1.7 vs 0.4%, respectively), and dizziness (1.1 and 0%, respectively). The most common adverse events with donepezil 23 mg/day compared to donepezil 10 mg/day were nausea (11.8 vs 3.4%, respectively), vomiting (9.2 vs 2.5%, respectively) and diarrhea (8.3 vs 5.3%, respectively). Serious adverse events occurred in 8.3% of patients receiving donepezil 23 mg/day and in 9.6% of patients receiving donepezil 10 mg/day. These included urinary tract infection (0.6 vs 0.4%, respectively), fall (0.6 vs 0.4%, respectively), pneumonia (0.3 vs 0.6%, respectively), syncope (0.2 vs 1.1%, respectively), aggression (0.2 vs 0.8%, respectively), and confusional state (0.1 vs 0.6%, respectively). Secondary: Not reported
Doody et al.[31] (2012) Donepezil 23 mg/day	DB, MC Patients with moderate-to-severe	N=not specified 24 weeks	Primary: Efficacy and safety	Primary: At week 24, donepezil 23 mg/day provided significant cognitive benefits over 10 mg/day (P<0.01) on the SIB, with or without concomitant memantine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs donepezil 10 mg/day Patients were allowed to also take memantine.	Alzheimer's disease		Secondary: Not reported	The higher dose showed no benefit on the global function, MMSE or ADL measures in either memantine subgroup. Rates of treatment-emergent adverse events were higher for donepezil 23 mg/day with memantine (80.7%) than 23 mg/day without memantine (69.7%) or 10 mg/day with/without memantine (66.7/62.0%); across all treatment groups, most events were mild/moderate in severity. Individual rates of serious adverse events were low (<1.0%), regardless of concomitant memantine use. Secondary: Not reported
Raskind et al.[32] (2004) Galantamine 24 mg/day	OL Patients with mild-to-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 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.[33] (2008) Galantamine 24 mg/day	MC, OL Patients with Alzheimer's disease who had received galantamine treatment for up to	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 from the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	36 months			Secondary: Not reported
Wallin et al.[34] (2011) Galantamine 24 mg/day	MC, OL, PRO Patients with Alzheimer's disease and no previous cholinesterase inhibitor therapy	N=280 36 months	Primary: MMSE, ADAS-cog, IADL, CIBIC Secondary: Subgroup analysis by K-means cluster analysis	Primary: From baseline to 36 months, MMSE decreased from 23.3 to 21.74. The MMSE score was significantly better at two months (P<0.001) and at six months (P=0.006) compared to baseline, and was stable at 12 months (P=0.616) compared to baseline. The total mean decline in MMSE score from baseline after three years of treatment was 2.6 From baseline to 36 months, ADAS-cog increased from 16.85 to 19.39. The total change in ADAS-cog score after three years of treatment was 5.6 points above baseline values. The ADAS-cog scores at 6 months were not different from baseline (P=0.248), but deteriorated after that. Mean IADL scores demonstrated deteriorated at all time points compared to baseline (12.76 to 17.13). According to CIBIC scores at two months, 93% of patients remaining in the study were "improved or unchanged", at months six, 12, 24, and 36, 81, 69, 50 and 41% of the patients were "improved or unchanged", respectively. Secondary: Cluster analysis identified two response clusters. Cluster 1 included patients with low ability in ADAS-cog and IADL scores at baseline. These patients were older and less educated, but responded better at six months compared to cluster two patients. Cluster 2 patients included better ADAS-cog and IADL scores at baseline. Cluster 2 patients had a higher frequency of the APOE ε4 allele.
Brodaty et al.[35] (2006) Galantamine 2 to 50 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe	N=345 ITT N= 229 PP 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	dementia		Secondary: Not reported	44% of ITT patients had an increased score at the six-month assessment as compared to baseline (P values were not reported). 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
Cummings et al.[36] (2004) Galantamine 8 to 24 mg/day vs placebo	DB, PC, RCT 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Scarpini et al.[37] (2011) Phase 1 Galantamine 8 to 16 mg/day Phase 2 Galantamine 16 mg/day vs placebo	Phase 1 MC, OL Phase 2 DB, MC, RCT Mild to moderate Alzheimer's disease in patients ≥50 years of age (MMSE, 11 to 24)	N=393 36 months	Primary: ADAS-cog/11 deterioration ≥4 points Secondary: CIBIC-plus, adverse events	Phase1 Primary: Cognitive functions improved significantly on the ADAS-cog/11 scale with galantamine treatment at month seven relative to baseline (from 24.1 to 22.9, difference, -1.2; 95% CI, -2.3 to -0.1; P<0.01). Scores were similar to baseline values at the end of the OL phase at month 12 (mean score at baseline, 24.1; mean score at month 12, 24.7; 95% CI, -0.5 to 1.7, P=0.16). Secondary: CIBIC-plus score improved in 34.3%, was unchanged in 30.9%, and worsened in 34.9% of patients when compared to baseline. A total of 50.4% of patients reported adverse events, of which the most common was gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%). Serious adverse events were reported in 12.2%. Phase 2 Primary: Patients receiving placebo were more likely to discontinue therapy prematurely compared to galantamine for any reason (HR, 1.76; 95% CI, 1.10 to 2.81; P=0.02) or lack of efficacy (HR, 1.80; 95% CI, 1.02 to 3.18; P=0.04). No significant difference was observed by ADAS-cog >4 between the groups (HR, 1.66; 95% CI, 0.78 to 3.54; P=0.19). Secondary: There were no significant differences between the treatment groups concerning mean values of the CIBIC-plus scale. A total of 34.1% of patients receiving galantamine and 27% of patients receiving placebo experienced adverse events. The most common adverse events were nervous system disorders (6.6%) and psychiatric disorders (5.3%). Serious adverse events were reported in 14.5% of galantamine-treated patients compared to 6.3% of patients in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kavanagh et al.[38] (2011) Galantamine 16 to 24 mg/day vs placebo	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=3,523 (5 trials) 5 to 6 months	Primary: Changes from baseline in ADAS-Cog 11 at trial endpoint (two to five months after reaching maintenance doses) Secondary: Not reported	Primary: The proportion of patients who met criteria for "improved", "stable", or "non-rapid decline" at trial endpoint were 45.8, 59.5, and 87.6%, respectively with galantamine compared to 27.2, 37.1, and 67.7%, respectively with placebo. Changes in ADAS-Cog 11 scores with galantamine were -4.9, -4.7 and -2.9 points, respectively, for "improved", "stable" and "non-rapid decline" compared to -3.6, -3.4, and -1.2, respectively with placebo. Patients receiving galantamine who were reported to be "improved" or "stable" experienced improvement in ADAS-Cog 11 scores until 18 months after starting treatment, and attenuated deterioration thereafter. For galantamine-treated patients exhibiting "non-rapid decline", mean ADAS-Cog 11 score returned to baseline after approximately 12 months. Secondary: Not reported
Burns et al.[39] (2009) Galantamine 24 mg/day vs placebo	DB, MC, PC, RCT Patients 40 to 95 years of age with severe dementia of the Alzheimer type or probable Alzheimer's disease (MMSE, 5 to 12 points)	N=407 6 months	Primary: SIB, MDS-ADL, and adverse events Secondary: Not reported	Primary: In the completer analysis, the mean total SIB score of the galantamine group increased to 69.1 points at week 26. The mean SIB score in the placebo group decreased to 66.9. The between group least squares mean difference was 4.36 (95% CI, 1.3 to 7.5; P=0.006). In the completer analysis, the mean total MDS-ADL self-performance score worsened in both groups: scores at week 26 were 13.0 points in the galantamine group and 13.6 points in the placebo group. The between-group least squares mean difference was –0.41 points (95% CI, –1.3 to 0.5; P=0.383). In the LOCF analysis, the mean SIB score in the galantamine group increased to 69.3 points. In the placebo group, the mean SIB score decreased by 3.2 points. The between-group least squares mean difference was 5.02 points (95% CI, 2.17 to 7.86; P=0.0006). In the LOCF analysis, the mean total seven-item MDS-ADL self-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				performance score in the galantamine group worsened at endpoint to 13.1 points and to 14.0 points in the placebo group. Changes from baseline in the seven-item MDS-ADL self-performance score were 1.3 points and 1.7 points, respectively. The between-group least squares mean difference was –0.50 (95% CI, –1.39 to 0.39; P=0.394). Significant between-group differences were seen in the galantamine group for memory (P=0.006), praxis (P=0.010), and visuospatial ability (P=0.002). There were no significant differences in language (P=0.064) or attention (P=0.075). Scores for all eleven-item MDS-ADL self-performance subscales worsened in both treatment arms. The deterioration in the subscale score for locomotion on unit was significantly less in the galantamine group (P=0.021). During the study, 88% of patients who received galantamine and 89% who received placebo had at least one adverse event. The most common adverse events in both treatment groups were urinary tract infections, vomiting, diarrhea, nausea, and falls. Secondary: Not reported
Raskind et al.[40] (2004) Galantamine 24 mg/day vs placebo	DB, PC, RCT 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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wilcock et al.[41] (2000) Galantamine 24 mg/day vs galantamine 32 mg/day 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.[42] (2006) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	Post hoc analysis, DB, MC, PC, RCT Patients with mild-to-moderate probable Alzheimer's disease	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[43] (2005) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	AC, DB, MC, PC, PG, RCT Patients with mild-to-moderate probable Alzheimer's disease	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 was significantly more effective with improvement from baseline in ADAS-cog/11 scores (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 group vs placebo (P=0.003; 95% CI, 0.85 to 4.03; LOCF; P<0.001; 95% CI, 1.09 to 3.91). In galantamine groups vs placebo, NPI scores were not statistically significant but instead numerically significant (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.
Loy et al.[44] (2006) Galantamine 8 to 36 mg/day vs	MA (10 trials) Patients diagnosed with mild cognitive impairment or Alzheimer's disease	N=6,805 12 weeks-2 years	Primary: CIBIC-plus, ADAS-Cog, ADCS-ADL, DAD, NPI Secondary:	Primary: Statistically significant difference was seen on the global rating scales for patients treated with galantamine, at all durations and all doses but 8 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Not reported	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
Herrmann et al.[45] (2011) Memantine 20 mg/day	OL Patients with moderate-to-severe Alzheimer's disease	N=31 3 months	Primary NPI-NH change in agitation and aggression subscale, CGI-C scale, caregiver impact, and effect on nursing burden measured by M-NCAS Secondary: Caregiver distress subscale of the NPI-NH, changes in psychotropic medications	Primary: There was a significant decrease in the NPI-NH agitation/aggression subscale score with memantine (P=0.014). According to the CGI-C scores, 48% of patients were improved (much improved or minimally improved). A total of 52% of patients did not benefit from treatment (no change, minimally worse or much worse). There was a significant decrease in the M-NCAS total score (P=0.005), as well as decreases on the attitude (P=0.009) and strain (P=0.013) subscales with memantine therapy. Secondary: The NPI-NH subscale score decreased significantly with memantine therapy (P=0.009). Psychotropic medications were available in 28 patients, with 64.3% receiving at least one dose during the study. Lorazepam was the most commonly used psychotropic (P=0.046). Overall, seven patients decreased psychotropic medication use during the study, while three increased usage; Most remained the same for psychotropic usage.
Bakchine et al.[46] (2007) Memantine 20 mg/day vs	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Not reported
Reisberg et al.[47] (2003) Memantine 20 mg/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 period (P=0.002).
Winblad et al.[48] (1999) Memantine 10 mg/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.[49] (2007) Memantine 20 mg/day	MA Four studies: memantine as monotherapy, 2	N=1,826 in subgroup with moderate-to-severe Alzheimer's	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	studies of memantine vs placebo in patients already taking an acetylcholinesterase inhibitor; patients diagnosed with moderate-to-severe Alzheimer's disease	disease 24 to 28 weeks	Secondary: Not reported	Secondary: Not reported
Wilkinson et al.[50] (2007) Memantine 20 mg/day vs placebo	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24 to 28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	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). 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
McShane et al.[51] (2006) Memantine 10 to 30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=3,731 (15 trials) Variable duration	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	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. 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Grossber et al.[52] (2013) Memantine extended-release 28 mg once daily vs placebo	DB, MC Outpatients with Alzheimer's disease (MMSE scores of 3 to 14)	N=677 24 week	Primary: Baseline-to-endpoint score change on the SIB and the endpoint score on the CIBIC-Plus. Secondary: Baseline-to-endpoint score change on the ADCS-ADL19; additional parameters included the baseline-to-endpoint score changes on the NPI and verbal fluency test	Primary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the SIB (2.6; 95% CI, 1.0 to 4.2; P=0.001) and CIBIC-Plus (P=0.008). Secondary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the NPI (P=0.005), and verbal fluency test (P=0.004); the effect did not achieve significance on ADCS-ADL19 (P=0.177). Adverse events with a frequency of >5.0 % that were more prevalent in the memantine group were headache (5.6 vs 5.1 %) and diarrhea (5.0 vs 3.9 %).
Burns et al.[53] (2004) 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 PDS, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the RR of dropping out due to adverse events was lower than in subjects with milder Alzheimer's disease. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dantoine et al.[54] (2006) Rivastigmine 3 to 12 mg/day Addition of memantine 5 to 20 mg/day was allowed for non-responders of rivastigmine at the 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) Total 28 weeks	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 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).
Olin et al.[55] (2010) Rivastigmine 6 to 12 mg/day and memantine	MC, OL, PRO Patients ≥50 years of age with moderate-to-severe	N=116 26 weeks	Primary: Safety and tolerability Secondary:	Primary: Nausea and vomiting occurred in 26.7 and 10.3% of patients, respectively. Most cases were mild with few severe cases reported (2.6 and 2.6%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg/day	Alzheimer's disease (MMSE ≥10 to ≤20)		ADCS-CGIC, ADCS-ADL measured	At least one treatment-emergent adverse event was experienced by 81.9% of patients. The most common adverse events were nausea (26.7%), dizziness (11.2%), vomiting (10.3%), and diarrhea (10.3%). No patients exhibited clinically significant ECG abnormalities. Secondary: At week 26, 59% of patients experienced no decline in MMSE total score from baseline. The mean change from baseline in MMSE total score was 0.7. At week 26, there was no change in global ADCS-CGIC scores. Patient and caregiver assessed mental/cognitive state, behavior and functioning severity scores were maintained to a similar extent throughout the study. The mean overall rating on the ADCS-CGIC was 4.0. At week 26, 64.5% of patients were considered unchanged or improved. The mean ADAS-ADL scores significantly declined by -2.9. At week 26, cognition, behavior and global functioning were unchanged or improved in 63.2, 71.1 and 77.6% of patients respectively.
Gauthier et al.[56] (2010) Rivastigmine 3 to 12 mg/day	MC, OL, OS, PRO Patients with mild-moderate Alzheimer's disease	N=3,800 12 months	Primary: Physician-assessed abbreviated CGI-C, MMSE, psychotropic medication use Secondary: Not reported	Primary: At six months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 46.4 vs 44.9 vs 8.8% for attention; 42.8 vs 50.0 vs 7.2% for apathy; 41.1 vs 49.5 vs 9.4% for anxiety; 33.8 vs 68.4 vs 7.7% for agitation; 35.1 vs 54.8 vs 10.1% for irritability; and 30.8 vs 63.8 vs 5.4% for sleep disturbance. At 12 months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 47.9 vs 41.0 vs 11.1 for attention; 44.1 vs 46.7 vs 9.2% for apathy; 41.8 vs 47.3 vs 10.9% for anxiety; 33.5 vs 57.6 vs 8.9% for agitation; 33.8 vs 56.4 vs 9.8% for irritability; and 29.7 vs 64.7 vs 5.6% for sleep disturbance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, CGI-C at six and 12 months demonstrated a larger percentage of patients with improvement vs deterioration. At six months, 54% of patients overall demonstrated no change. At 12 months, 52% of patients overall demonstrated no change. MMSE scores were 20.8 at baseline, 21.5 after three months, 21.3 after six months, and 21.3 after 12 months. At baseline, 61.3% of patients were not taking a psychotropic medication. At six months, the proportion of patients not taking any psychotropic medications increased to 70.8%; at 12 months, it was 84.7%.
Birks et al.[57] (2000) 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, abdominal pain and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Birks et al.[58] (2009) Rivastigmine vs placebo	MA Patients diagnosed with probable Alzheimer's disease	N=4,775 (9 trials) Variable duration	Primary: Cognitive function, global impression, activities of daily living, behavioral disturbance, withdrawal	Primary: <u>Cognitive function</u> The meta-analysis, using WMD, demonstrated benefit on cognitive function as measured by ADAS-Cog test scores for rivastigmine compared to placebo as follows: rivastigmine 1 to 4 mg/day at 18 weeks (WMD, -1.07; 95% CI, -1.66 to -0.48; P=0.0004) and 26 weeks (WMD, -0.84; 95% CI, -1.48 to -0.19; P=0.01); rivastigmine 6 to 12 mg/day at 12 weeks (WMD, -1.49; 95% CI, -1.96 to -1.01; P<0.00001), 18 weeks (WMD, -1.79; 95% CI, -2.30 to -1.29;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rates, and incidence of adverse effects Secondary: Not reported	P<0.00001) and 26 weeks (WMD, -1.99; 95% CI, -2.49 to -1.50; P<0.00001). An additional analysis of ADAS-Cog dichotomized into those showing less than four points improvement and those showing four or more points improvement at 26 weeks shows benefit for cognitive function for the 6 to 12 mg daily of rivastigmine compared to placebo (83% did not show four points improvement compared to 89%; OR, 0.6; 95% CI, 0.4 to 0.8). There was no difference for the 1 to 4 mg/day dose compared to placebo (88% did not show four points improvement compared to 90%; OR, 0.84; 95% CI, 0.60 to 1.19). MMSE shows similar results in favor of rivastigmine at 26 weeks compared to placebo as follows: rivastigmine 1 to 4 mg/day at 26 weeks (WMD, 0.43; 95% CI, 0.08 to 0.78; P=0.02) and rivastigmine 6 to 12 mg/day at 26 weeks (WMD, 0.82; 95% CI, 0.56 to 1.08; P<0.00001). One study used the SIB, which shows benefit associated with higher dose rivastigmine compared to placebo at 26 weeks (WMD, 4.53; 95% CI, 0.47 to 8.59; P=0.03). Global assessment Using the CIBIC-Plus scale or the ADCS-CGIC scale, there were benefits associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 0.74; 95% CI, 0.60 to 0.92; P=0.008), 18 weeks (OR, 0.79; 95% CI, 0.64 to 0.98; P=0.03) and at 26 weeks (OR, 0.66; 95% CI, 0.55 to 0.79; P<0.00001); rivastigmine 1 to 4 mg/day at 26 weeks (OR, 0.71; 95% CI, 0.55 to 0.93; P=0.01). Using GDS, there were benefits associated with rivastigmine 6 to 12 mg/day compared to placebo (55% showed the worse condition compared to 59%; OR, 0.78; 95% CI, 0.64 to 0.94; P=0.01) but not with 1 to 4 mg daily rivastigmine compared to placebo. ADL The PDS showed an improvement associated with rivastigmine compared

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				to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (WMD, 1.08; 95% CI, 0.19 to 1.98; P=0.02), 18 weeks (WMD, 1.90; 95% CI, 0.93 to 2.88; P=0.0001), and 26 weeks (WMD, 2.15; 95% CI, 1.13 to 3.16; P<0.0001). One study assessing ADL using the ADCS-ADL scale and showed benefit for rivastigmine 6 to 12 mg/day at 24 weeks (WMD, 1.80; 95% CI, 0.20 to 3.40; P=0.03). Behavioral disturbance There was no difference between rivastigmine and placebo in behavioral disturbance found in two studies using the neuropsychiatric instrument (NPI-10, and NPI-12). Withdrawals before the end of treatment There were no significant differences in withdrawal rates with rivastigmine 1 to 4 mg/day and placebo at 12, 18 and 26 weeks. There were significant differences in withdrawal rates for the higher dose group in favor of placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 2.60; 95% CI, 1.19 to 5.68; P=0.02), 18 weeks (OR, 4.02; 95% CI, 1.31 to 12.32; P=0.01), and 26 weeks (OR, 2.19; 95% CI, 1.83 to 2.63; P<0.00001). Adverse events There were no significant differences in the numbers of patients with at least one adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg/day) and placebo groups in favor of placebo by the end of the titration period (OR, 2.96; 95% CI, 2.39 to 3.68; P<0.00001) and by 26 weeks (OR, 2.49; 95% CI, 2.05 to 3.02; P<0.00001). There were no significant differences in the numbers of patients with at least one severe adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg daily) and placebo groups in favor of the placebo group for the titration period (OR, 1.88; 95% CI, 1.39 to 2.55;

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				P<0.0001). There were significant differences, in favor of placebo, for the rivastigmine 6 to 12 mg/day group by the end of the titration period, and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favor of placebo, for the rivastigmine 1 to 4 mg/day group by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, and anorexia. Secondary: Not reported
Rosler et al.[59] (1999) 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	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 to 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).

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Articus et al.[60] (2011) Rivastigmine patch 9.5 mg/24 hours	MC, OL Patients with Alzheimer's disease	N=208 24 weeks	Primary: Proportion of patients treated with rivastigmine for ≥8 weeks at week 24 Secondary: Tolerability, week 24 MMSE, ADCS-CGIC, ADCS-ADL, ADCPQ, Zarit Burden Interview Score	Primary: In the ITT population, 80.8% of patients (95% CI, 75.0 to 86.5) were treated for at least eight weeks with rivastigmine. A total of 74.2% of patients (95% CI, 67.8 to 80.5) were treated for at least eight weeks and completed the study. A total of 74.2% of patients treated rivastigmine patch were able to reach and maintain the maximum dose for at least eight weeks. The most common adverse events being nausea (10.1%), erythema (8.7%), pruritus (8.2%), and vomiting (7.2%). Secondary: The most common adverse events were nausea (10.1%), erythema (8.7%), pruritus (8.2%), vomiting (7.2%), diarrhea (4.3%) and agitation (4.3%). At week 24, improvements were seen on: MMSE (1.3), and ADCS-ADL (1.3). At week 24, improvements in ADCS-CGIC were demonstrated in 34.6% of patients as assessed by patients, and in 29.7% of patients as assessed by the caregiver. ADCPQ scores improved 18.5 points, and Zarit Burden Interview Score improved slightly at each visit until week 24 (-0.4).
Grossberg et al.[61] (2009) Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours	OL Patients 50 to 85 years of age with Alzheimer's disease (MMSE scores 10 to 20)	N=870 28 weeks (weeks 25 to 52 of open-label extension)	Primary: Safety and tolerability Secondary: ADAS-cog	Primary: During the first four weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer adverse events than those formerly randomized to placebo (≤15.2 vs 28.2%). This prior exposure effect was noted for nausea (≤2.5 vs 8.5%) and vomiting (≤1.9 vs 6.0%). A total of 57.6% of patients reported adverse events during the OL extension (weeks 25 to 52), with nausea and vomiting being reported most frequently (15.7 and 14.3%, respectively). During the OL extension, over 90% of all patients experienced "no, slight,

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				or mild'' skin irritation as their most severe application-site reaction. The symptoms that were most commonly reported as moderate or severe were erythema and pruritus (7.7 and 5.6%, respectively). Serious adverse events occurred in 1.0% of patients during the first four weeks of the OL extension phase (weeks 25 to 28) and 9.4% of patients during the full open-label extension phase (weeks 25 to 52). The most common serious adverse events were gastrointestinal disorders (2.0%), infections and infestations (2.0%), cardiac disorders (1.7%), and nervous system disorders (1.5%). Eight deaths occurred during the OL extension phase and a further two occurred during the 30-day follow-up period. The causes of death were most commonly cardiac disorders (n=5) and nervous system disorders (n=3). None were considered treatment related. Secondary: Patients previously randomized to placebo who were switched to the 9.5 mg/24 hour rivastigmine patch during the OL extension experienced a 1.3-point increase in their ADAS-cog scores during weeks 24 to 40. There was no overall change in ADAS-cog score at week 40 compared to baseline (95% CI, -1.4 to 0.6). The increase in ADAS-cog score was not sustained beyond week 40. Patients receiving rivastigmine treatment for the entire study (weeks 0 to 52) showed a deterioration of 0.3 points (95% CI, -0.4 to 0.9) on the ADAS-cog at week 52. Those receiving placebo for weeks 0 to 24, followed by the patch, showed a deterioration of 0.9 points [95% CI, -0.4 to 2.1).
Gauthier et al.[62] (2013) Rivastigmine transdermal patch 4.6 mg/24 hours or 9.5 mg/24 hours, once daily	OS Patients with Alzheimer's disease with MMSE score of 10 to 26 and GDS score of 4 to 6	N=1,204 18 months	Primary: Change in MMSE from baseline to 18 months Secondary: Change in	Primary: Over 18 months of treatment there were no clinically significant changes in MMSE. Secondary: Over 18 months of treatment there were no clinically significant changes in GDS.

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			MMSE at six and 12 months and change in GDS, assessment of patient ability, overall patient assessment rating, caregiver-reported compliance and treatment satisfaction at six, 12, and 18 months	The majority of patients showed improvement or no change in GDS, assessment of patient ability and overall patient assessment rating over 18 months. The proportion with reported improvement in GDS, assessment of patient ability and overall patient assessment rating was higher than the proportion that deteriorated. Compliance improved from baseline to 18 months and for 88.2% of patients caregivers preferred the transdermal patch to oral medications.
Sadowsky et al.[63] (2010) US13 and US18 Rivastigmine capsules 3 to 12 mg/day US38 Rivastigmine patch 4.6 mg/24 hours for 5 weeks, then rivastigmine patch 9.5 mg/24 hours for 20 weeks	US13 and US18 PRO, MC, OL US38 RCT, MC, OL Patients ≥49 years of age with a diagnosis of dementia of the Alzheimer type (MMSE ≥8 to ≤26 or MMSE ≥10 to ≤24) who showed a poor response to donepezil	N=592 25 to 26 weeks	Primary: Safety and tolerability	Primary: In US13 and US18, 67.7% of patients completed the studies and 32.3% of patients withdrew due to adverse events (59.8%), unsatisfactory treatment effect (15.9%), withdrawal of consent (15%), and loss to follow-up (6.5%). The remaining 2.7% of patients discontinued due to protocol deviation, administrative problem, or death. In US13 and US18, the most frequently reported adverse events (AEs) were nausea (32.9%), vomiting (24.1%), dizziness (11.8%), weight loss (9.1%) agitation (7.9%), fall (7.9%) and confused state (7.9%). Serious AE's were reported in 6% of patients and included pneumonia (1.8%), syncope (1.2%), dehydration (1.2%) and vomiting (1.2%). In US38, 67.4% of patients completed the study. The primary reasons for not completing the study were adverse events (44.7%), withdrawal of consent (29.4%), unsatisfactory treatment effect (10.6%), protocol deviation (7.1%), and loss to follow-up (3.5%). The remaining 4.7% of patients discontinued due to administrative problems, abnormal test procedure, or death.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In US38, 70.5% of patients reported at least 1 AE. More patients in the immediate-switch group (73.3%) experienced at least one AE during the study than in the delayed-switch group (67.7%). The most common adverse events were application site reaction (15.3%), and agitation (6.9%). The most common serious AEs reported were syncope (1.1%), dehydration (0.8%) and pneumonia (0.4%). Discontinuation due to AE (14.6%) was the most common reason for patients not completing the extension phase in both immediate- and delayed-switch groups; the differences between the groups were NS. Discontinuations occurred for the following reasons: application site reaction (4.2%), disease progression (2.3%), and agitation (1.5%). Discontinuation due to gastrointestinal AEs was lower for the rivastigmine patch compared to the capsules.
Cummings et al.[64] (2012) 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, and change in the NPI-10, and the NPI-caregiver distress scale.	Primary: The 13.3 mg/24 hours patch was statistically superior to the 9.5 mg/24 hours 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 hours 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 hours patch group compared to 81.2% with the 9.5 mg/24 hours patch Group. The difference was not statistically significant. Patients in the 13.3 mg/24 hours patch group had smaller increases in time to complete the Trail Making Test parts A at weeks 24 and 48 compared to those in the 9.5 mg/24 hours 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.

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				The most frequently reported adverse events by primary system organ class were gastrointestinal disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 hours 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 hours than the 9.5 mg/24 hours patch (2.1 vs 6%).
Cummings et al.[65] (2010) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs placebo	DB, PC, PRO, RCT Patients 50 to 85 years of age with mild-to-moderate Alzheimer's disease	N=1,195 24 to 52 weeks	Primary: Tolerability at 24 weeks Secondary: Patients skin condition at the application site at 28 weeks	Primary: No serious skin reactions were reported in either the 24 or 28 week phases of the study. During the 24 week period, 574 patients wearing an active patch and 579 patients wearing a placebo patch underwent at least one assessment of application-site skin condition. Of patients on the 9.5 mg/24 hour patch, erythema and pruritus were the most commonly reported reactions (moderate in 7.6% of patients and severe in 6.7% of patients). A total of 89.6% of patients in the patch group had "no, slight, or mild" signs and symptoms for their most severe application site reaction. Secondary: A total of 870 patients entered the 28 week phase of the study and received rivastigmine 9.5 mg/24 hours patch. Overall, the skin tolerability profile was similar to the DB phase. A total of 91.5% of patients experienced "no, slight, or mild" symptoms as their most severe application site reaction, with erythema and pruritus being the most common finding. A total of 3.7% of patients discontinued treatment due to skin reactions during the open-label extension, and there was no increase in the severity of skin reaction noted.
Molinuevo et al.[66] (2012) Rivastigmine patch 9.5 mg/24 hours	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=649 6 months	Primary: Adherence rates Secondary: Strategies followed by a physician to	Primary: At baseline, 0.6% of patients were taking ≥80% of their medication as prescribed. At three and six months, 77 and 88.1%, respectively, were noted to be taking more than 80% of their medication as prescribed (P<0.0001 vs baseline). The proportion of adherent patients at three months was 73.6% and at six months was 85.9% (P<0.0001).

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vs rivastigmine 3 to 12 mg/day			improve adherence and reasons for nonadherence reported by patients	Secondary: Modification of Alzheimer's disease treatment was the only intervention that substantially improved adherence at three months (P<0.0001). At the six month visit, psychoeducation was the only effective strategy that reached statistical significance (P<0.0001). The most common reasons for nonadherence include forgetfulness (56.4%), avoidance of adverse events (30.7%), and refusal of treatment (25.3%).
Boada et al.[67] (2013) Rivastigmine transdermal patch vs rivastigmine capsules	OL Patients treated with rivastigmine	N=1,078 Duration not specified	Primary: Patient satisfaction (Treatment Satisfaction with Medicines and the Morisky-Green questionnaires) Secondary: Not reported	Primary: Satisfaction reported was greater with transdermal than oral rivastigmine: mean+standard deviation of the total Treatment Satisfaction with Medicines score, 72.5+14.1 vs 65.2+12.5; P<0.001. The proportion of adherent patients was greater with transdermal than with oral rivastigmine (65.0 vs 41.4%; P<0.001). Satisfaction, in turn, was significantly greater in adherent cases than in nonadherent cases. Secondary: Not reported
Blesa González et al.[68] (2011) Rivastigmine 6 to 12 mg/day (RO) vs rivastigmine patch titrated to 9.5 mg/24 hours (RPT) vs	MC, OL, RCT Patients ≥60 years of age with mild-to-moderate Alzheimer's disease who were previously treated with oral rivastigmine	N=142 3 months	Primary: Gastrointestinal adverse events Secondary: Overall tolerance, local tolerance for those patients on patches, satisfaction level, and cognitive state by MMSE	Primary: Gastrointestinal adverse events were reported in <5% of patients receiving patches (4.7% in RPT and 4.3% in RP) vs 6.1% in RO patients. No statistical significance was reached (P=0.8667). Gastrointestinal adverse events were noted in 11 cases, two in RPT patients, six in RP patients, and three in the RO patients (P=0.3067). Secondary: Overall tolerability did not reveal any significant differences among the groups (P=0.8239). Local tolerability revealed skin or subcutaneous tissue adverse events reported in 11.6% of patients in the RPT group vs 17% of patients in the RP group (P=0.4055). All skin adverse events were reported as slight or

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rivastigmine patch 9.5 mg/24 hours (RP)				moderate intensity. RP was defined by 72% of patients as very easy to use, while RO was considered very easy to use by 30% of patients (P=0.0005). In RP patients, 67% considered it very easy to follow compared to 19% of RO patients (<0.0001). A total of 72% of RP patients confirmed the treatment never interfered with their daily lives vs 40% of the RO group (P=0.0085). Overall satisfaction comparisons revealed that in RP patients, 60% were very satisfied vs 14% in RO patients (P<0.0001). MMSE did not demonstrate significant differences among treatment groups when compared at one and three month visits.
Winblad et al.[69] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	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 Test part A	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).
Winblad, Kawata et al.[70] (2007)	DB, DD, PC ACs included	N=1,059 24 week	Primary: ADCPQ	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001).

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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	different size rivastigmine patches and rivastigmine capsules		Secondary: Not reported	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 et al.[71] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs	DB, DD, MC, PG Women or men 50 to 85 years of age with a diagnosis of dementia of the Alzheimer's type according to the DSM-IV, and probable Alzheimer's disease	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI for behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive	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 cm^2 patch and capsule group (all P<0.05 vs placebo). The 20 cm^2 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

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placebo			functions; Trail Making Test Part A for assessment of attention, visual tracking and motor processing speed	different from those in the placebo groups (all P>0.05).
Blesa et al.[72] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DB, DD, PC ACs 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 eight 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
Farlow et al.[73] (2011) Rivastigmine patch 9.5 mg/24 hours vs	RETRO Patients with mild-to-severe Alzheimer's disease	N=1,050 24 weeks	Primary: ADAS-cog, ADCS-CGIC, and ADCS-ADL Secondary: Not reported	Primary: In patients with moderate disease, there was a significant improvement on ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0009) and rivastigmine capsule (P=0.0128). For patients with moderately severe disease, there was a significant improvement in ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.006), rivastigmine 9.5 mg/24 hour patch (P=0.0163), and

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rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo				rivastigmine capsule (P=0.0071) compared to placebo. For patients with severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 9.5 mg/24 hour patch (P=0.037) and rivastigmine capsule (P=0.0073) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 17.4 mg/24 hour patch (P=0.043) and rivastigmine 9.5 mg/24 hour patch (P=0.0116) compared to placebo. Significant improvement on ADCS-CGIC scores were seen with the rivastigmine 17.4 mg/24 hour patch in patients with moderate disease (P=0.03) and mild to moderate disease (P=0.0455) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0211) compared to placebo. For patients with moderate disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0194) and rivastigmine capsule (P=0.0077) compared to placebo. There was no significant difference in ADCS-ADL scores among the treatment groups in patients with severe AD.
Choi et al.[74] (2011) Rivastigmine patch 4.6 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours and	MC, OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=172 24 weeks	Primary: Tolerability Secondary: Efficacy as measured by CMAI-K, ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB scores	Primary: The incidence of adverse events (53.4 vs 50.6%) and discontinuation due to adverse events (6.8 vs 4.8%) was not different between patients with and without memantine, respectively. The most common adverse events were skin irritation in both treatment groups (42 vs 34.9%; P=0.71), but discontinuation was rare (4.5 vs 2.4%; P=0.74). Secondary: CMAI-K scores favored rivastigmine monotherapy vs combination therapy

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memantine 5 mg/day titrated to 20 mg/day vs rivastigmine patch 9.5 mg/24 hours				at the end of treatment (P=0.01). Changes in other efficacy measures (ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB) were not significantly different.
Farlow et al.[75] (2010) Rivastigmine patch 9.5 mg/24 hours and memantine vs rivastigmine patch 9.5 mg/24 hours	OL, RCT Patients ≥50 years of age with mild-to-moderate Alzheimer's disease who had been receiving donepezil for at least 6 months and at a stable dose of 5-10 mg/day for a minimum of 3 months	N=261 25 weeks	Primary: Safety and tolerability of rivastigmine transdermal patch, with or without concomitant memantine Secondary: Changes in cognition, global functioning and activities of daily living measured by MMSE and ADCS-ADL using the CGIC	Primary: The incidences of adverse events (73.3 vs 67.5%) and serious adverse events (10.4 vs 7.1%) were both slightly higher in patients receiving concomitant memantine, but the differences were NS (95% CIs, -5.2 to 16.9 and -3.6 to 10.1 for adverse events and serious adverse events, respectively). The most frequent adverse events in the combination therapy group and the rivastigmine monotherapy group were application site reactions (17.5 vs 13.5%, respectively) and agitation (5.9 vs 7.9%, respectively). Secondary: Concomitant memantine was associated with no significant changes in efficacy, as assessed by CGIC and MMSE scores. Global functioning remained unchanged or improved (CGIC rating ≤4) in 57.7 and 67.2% of patients with memantine and patients without memantine, respectively (P=0.604). ADCS-ADL scores deteriorated from baseline in both groups, with significant worsening in patients receiving memantine compared to those not receiving memantine (mean change from baseline rivastigmine and memantine vs rivastigmine monotherapy: -5.3 vs -2.0; P=0.043).
Harry et al.[76] (2005) Donepezil with doses ranging from 5 to 10 mg/day	MA Patients with mild-to-moderate Alzheimer's disease, and without diagnosis of any	N=3,353 3 donepezil studies 5 galantamine	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or galantamine with doses ranging from 8 to 36 mg/day vs placebo	other psychiatric or neurological disorder	studies Duration varied		
Wilcock et al.[77] (2003) Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary: MMSE, ADAS-Cog, NPI	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. Secondary: 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).The between group difference in MMSE change did not reach statistical significance. In the ADAS-Cog analysis, between group differences for the total population were NS, whereas galantamine treated patients with MMSE scores of 12 to 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.
Jones et al.[78] (2004) Donepezil 10 mg/day vs	OL, RCT Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
galantamine 12 mg twice daily			living Secondary: Not reported	Activities of daily living improved significantly in the donepezil group compared to the galantamine group at weeks four and 12 (P<0.05). Forty-six percent of galantamine patients reported gastrointestinal adverse events vs 25% of donepezil patients. Secondary: Not reported
Modrego et al.[79] (2010) Donepezil 10 mg/day vs memantine 20 mg/day	PG, RCT, SB Patients with mild-to-moderate Alzheimer's disease	N=63 6 months	Primary: ADAS-cog, NPI, DAD, changes in N-acetylaspartate metabolite levels Secondary: Not reported	Primary: There were no significant differences in the clinical scales with donepezil and memantine (donepezil: ADAS-cog, -0.12; P=NS, NPI, -0.04; P=NS, DAD, 6.67; P=0.014) (memantine: ADAS-cog, -1.37; P=NS, NPI, 1.25;P=NS, DAD, 4.46; P=NS). More patients worsened than improved on either drug. Daily living activities decreased by 4.4% in the memantine group and 6.6% in the donepezil group (P=0.6). At baseline, N-acetylaspartate/Cr ratio in the PCG correlated significantly with the ADAS-cog (P=0.02) and MEC (P=0.02). The N-acetylaspartate/Cr ratio correlated with the baseline ADAS-cog (P=0.02) in the left temporal lobe. At week 24, the PCG was the only area where the correlation was significant. The patients who improved in the ADAS-cog showed increases in the N-acetylaspartate/Cr ratios (P=0.004). None of the baseline metabolite levels predicted response to treatment in any of the examined areas. Secondary: Not reported
Wilkinson et al.[80] (2002) Donepezil 10 mg/day	OL, RCT Patients with mild-to-moderate	N=111 12 weeks	Primary: ADAS-Cog, tolerability	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rivastigmine 6 mg twice daily	Alzheimer's disease		Secondary: Not reported	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
Van Puyvelde et al.[81] (2011) Galantamine vs donepezil or rivastigmine (safety control group)	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=128 6 months	Primary: Safety, patients and caregiver satisfaction, global impression as reported by the physician Secondary; Not reported	Primary: Adverse events were similar among both treatment groups (galantamine, 34%; SCG, 34.4%). The incidence of serious (12 events) and severe (15 events) adverse events with galantamine was similar to the SCG group (serious: galantamine 9.3% vs safety control group 9.7%); severe: galantamine 11.3% vs safety control group 12.9%. A total of 84.5% of patients treated with galantamine continued their treatment after six months. Patients receiving galantamine reported their condition as improved (49%), unchanged (47%) and worsened (4%). Caregivers rated global evaluation as better (37%), unchanged (41%) and worse (22%) with galantamine. Physicians rated global clinical impression of change as better (46%), unchanged (34%) and worse (20%) with galantamine. Measurements of cognition and behavior remained stable. The appreciation of physicians and caregivers corresponded well (P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tariot et al.[82] (2004) Memantine 20 mg/day vs donepezil	DB, MC, PC, RCT 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: Not reported
Bullock et al.[83] (2005) Rivastigmine 3 to 12 mg/day vs donepezil 5 to 10 mg/day	DB, MC, RCT Patients 50 to 85 years of age with moderate to moderately-severe Alzheimer's disease (MMSE score 10-20)	N=994 24 months	Primary: SIB Secondary: GDS, ADCS-ADL, MMSE, NPI	Primary: Donepezil-treated patients declined 9.91 points from baseline on the SIB as compared to rivastigmine-treated patients, who declined by 9.30 points (P=NS). Secondary: Rivastigmine was more effective than donepezil on the ADCS–ADL, on which there was a between-treatment difference of 2.1 points after two years (P=0.007), and greater efficacy on the GDS (P=0.049). There were no significant differences in MMSE and NPI between the treatment groups. More patients receiving rivastigmine reported 'any adverse event' compared to those receiving donepezil during the titration phase (82.0 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				64.7%, respectively). Adverse events were higher with rivastigmine during the titration phase and included nausea (32.9 vs 15.2%) and vomiting (27.9 vs 5.8%). In the maintenance phase, adverse event rates in the two groups were similar (78.7% for the rivastigmine group and 76.9% for the donepezil group). Premature discontinuations due to adverse events were higher in the rivastigmine group during the titration phase (14.1 vs 7.0% for donepezil) but similar in the maintenance phase (17.9 vs 14.1% for donepezil).
Mossello et al.[84] (2004) Donepezil 5 to 10 mg/day vs galantamine 16 to 24 mg/day vs rivastigmine 6 to 12 mg/day	OL, OS Patients with mild-to-moderate Alzheimer's disease	N=407 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 patients). 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.[85] (2004) Donepezil vs galantamine vs rivastigmine	OL Patients 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. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lopez-Pousa et al.[86] (2005) Donepezil vs galantamine vs rivastigmine vs historical controls	OL, PRO Patients with mild-to-moderate Alzheimer's disease	N=147 6 months	Primary: MMSE Secondary: Not reported	Primary: All three 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
Rodda et al.[87] (2009) Donepezil 5 to 10 mg/day vs galantamine 8 to 24 mg/day vs rivastigmine 9 to 17.4 mg/day	RETRO Patients with Alzheimer's disease being treated with donepezil, rivastigmine or galantamine monotherapy	N=6,110 12 to 170 weeks	Primary: NPI Secondary: Not reported	Primary: Three of the 14 studies reviewed reported statistically significant improvement in overall NPI score or in the agitation/aggression item of the NPI only. One study demonstrated a significant difference in NPI score between groups randomized to either continuation or discontinuation of donepezil (placebo following an initial OL treatment phase. Of these four positive studies, two specified a minimum level of behavioral disturbance at baseline and used behavioral scores as a primary outcome. Secondary: Not reported
Howard et al.[88] (2012)	DB, MC, RCT Community-based	N=295 52 weeks	Primary: Standardized Mini-Mental	Primary: Mean donepezil vs placebo Standardized Mini-Mental State Examination scores were higher with donepezil (better cognitive function) by an average

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 10 mg/day vs memantine 20 mg/day vs donepezil 10 mg/day and memantine 20 mg/day vs placebo	patients with moderate-to-severe Alzheimer's disease who were taking donepezil 10 mg/day for ≥3 months		State Examination and BADLS scores Secondary: NPI, caregiver health status assessed by General Health Questionnaire 12	of 1.9 points (95% CI, 1.3 to 2.5; P<0.001) and BADLS scores were lower (less functional impairment) by 3.0 points (95% CI, 1.3 to 2.5; P<0.001). Both outcomes demonstrated significant heterogeneity in treatment efficacy over tome (P=0.002 and P=0.004, respectively), with less benefit apparent at the six week assessment than at later time points. From six weeks onward, differences were roughly parallel. Mean donepezil+memantine vs placebo+memantine Standardized Mini-Mental State Examination scores were higher with donepezil by an average of 1.2 points (95% CI, 0.6 to 1.8; P<0.001) and BADLS scores were lower by 1.8 points (95% CI, 0.3 to 2.8; P<0.001). Both outcomes were smaller than the minimum clinically important difference. Interactions of memantine therapy with visit were NS. Both donepezil and memantine demonstrated benefits on both Standardized Mini-Mental State Examination and BADLS larger in the absence of other agents alone, though statistically insignificant (P=0.14 and P=0.09, respectively). No significant benefits were seen adding memantine to donepezil on Standardized Mini-Mental State Examination scores (0.8 points higher with memantine and placebo; 95% CI, -0.1 to 1.6; P=0.07) or BADLS scores (0.5 points lower with memantine than placebo; 95% CI, 2.2 to 1.2; P=0.57). Secondary: NPI scores were lower for patients on memantine compared to placebo, indicating fewer behavioral and psychological symptoms by 4.0 points (99% CI, 0.6 to 7.4; P=0.002). No observable NPI differences noted with continuation, as compared to discontinuation of donepezil therapy (2.3 points lower with continuation; 95% CI, -1.1 to 5.7; P=0.08). Donepezil+memantine vs donepezil demonstrated a lower NPI score by 5.1 points (99% CI, 0.3 to 9.8; P=0.006). Continuation of donepezil and donepezil+memantine compared to the placebo and memantine + placebo demonstrated larger average decreases

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(indicating fewer psychological symptoms) across trial visits in General Health Questionnaire 12 scores for caregiver health status. There was a 0.5 point larger decrease with continuation vs discontinuation of donepezil (99% CI, -0.01 to 1.0; P=0.01) and 0.5 point larger decrease with memantine vs placebo (95% CI, -0.1 to 0.9; P=0.03), though significance was not reached to allow for multiple secondary outcomes.
Porsteinsson et al.[89] (2008) Memantine 20 mg/day plus cholinesterase inhibitor vs cholinesterase inhibitor plus 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.
Cumming et al.[90] (2006) Memantine 20 mg/day plus donepezil vs donepezil	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
Maidment et al.[91] Memantine 20 mg daily vs	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or memantine 20 mg daily in combination with a cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)				
Wilkinson et al.[92] (2009) Cholinesterase inhibitors (donepezil 5 or 10 mg/day) vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	N=906 (3 trials) 24 weeks	Primary: MMSE Secondary: Not reported	Primary: A significantly greater percentage of placebo patients than donepezil-treated patients met the specified criteria for all three definitions of clinical worsening. The OR for clinical worsening were significantly reduced for donepezil-treated patients compared to placebo patients (P<0.0001 for all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. This outcome was also apparent when milder (MMSE, 18 to 26) and more moderate (MMSE, 10 to 17) subgroups were analyzed separately. Secondary: Not reported
Feldman et al.[93] (2009) Cholinesterase inhibitors	OS, PRO Alzheimer's disease patients with and without cerebrovascular disease	N=548 7 years	Primary: Time to nursing home placement Secondary: Identify factors noted to reduce	Primary: The overall median time to permanent institutional admission was 42.4 months (95% CI, 38.0 to 48.0 months). Secondary: Factors noted to reduce the risk of being admitted to a nursing home included higher baseline DAD and MMSE scores, Alzheimer's disease

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			risk of NHP, including measurement of DAD and MMSE	diagnosis, living with caregiver, country, and treatment duration (P<0.05). Each year of treatment demonstrated a reduced risk of nursing home admission (galantamine, -31%, other cholinesterase inhibitors, -29%).
Trinh et al.[94] (2003) Cholinesterase inhibitors vs placebo	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one month with a cholinesterase inhibitor	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). Cholinesterase inhibitors improved IADL statistically compared to placebo (95% CI, 0.01 to 0.17). Secondary: Not reported
Lanctot et al.[95] (2003) Cholinesterase inhibitors 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Birks et al.[96] (2006) Cholinesterase inhibitors vs placebo	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 to six months, adverse events	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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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: 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).
Hansen et al.[97] (2008) Cholinesterase inhibitors	MA Patients with Alzheimer's disease	26 trials Variable duration	Primary: Cognition (ADAS-cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C) Secondary: Not reported	Primary: <u>Cognition (14 studies)</u> The pooled WMD in change between active treatment and placebo was -2.67 (95% CI -3.28 to -2.06) for donepezil, -2.76 (95% CI -3.17 to -2.34) for galantamine, and -3.01 (95% CI -3.80 to -2.21) for rivastigmine. <u>Function (14 studies)</u> The pooled standardized mean difference between active treatment and placebo was 0.31 (95% CI, 0.21 to 0.40) for donepezil, 0.27 (95% CI, 0.18 to 0.36) for galantamine, and 0.26 (95% CI, 0.11 to 0.40) for rivastigmine. <u>Behavior (seven studies)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The pooled WMD in NPI score between active treatment and placebo was -4.3 (95% CI, -5.95 to -2.65) for donepezil and -1.44 (95% CI, -2.39 to -0.48) for galantamine. Global assessment of change (nine studies) The pooled RR of responding for active treatment compared to placebo was 1.88 (95% CI, 1.50 to 2.34) for donepezil, 1.15 (95% CI, 0.96 to 1.39) for galantamine, and 1.64 (95% CI, 1.29 to 2.09) for rivastigmine. Secondary: Not reported
Kim et al.[98] (2011) Cholinesterase inhibitors	MA Cognitively impaired older adults	54 trials Variable duration	Primary: Falls, syncope, fracture and accidental injury reported Secondary: Not reported	Primary: Cholinesterase inhibitors usage was associated with the greatest risk of syncope compared to placebo (OR, 1.53; 95% CI, 1.02 to 2.30), but not with any other events: falls (OR, 0.88; 95% CI, 0.74 to 1.04); fracture (OR, 1.39; 95% CI, 0.75 to 2.56); accidental injury (OR, 1.13; 95% CI, 0.87 to 1.45). Memantine was associated with fewer fractures (OR, 0.21; 95% CI, 0.05 to 0.85), but not with other events: falls (OR, 0.92; 95% CI, 0.72 to 1.18), syncope (OR, 1.04; 95% CI, 0.35 to 3.04); accidental injury (OR, 0.80; 95% CI, 0.56 to 1.12). There were no differential effects noted according to type and severity of cognitive impairment, residential status, or length of follow-up.
Parkinson's Disease				
Emre et al.[99] (2004) Rivastigmine 3 to 12 mg/day; average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease	N=541 Dose titration over the first 16 weeks with a subsequent assessment period of 8 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR power of attention tests, D-KEFS verbal	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		Total of 24 weeks	fluency test, Ten Point Clock-drawing Test	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.[100] (2005) Rivastigmine 3 to 12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years old with Parkinson's disease	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. Reaction time variability continued to show improvement over placebo from week 16 (P<0.05) to week 24 (P<0.001). Secondary: Not reported
Schmitt et al.[101] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients with Parkinson's disease dementia	N=541 24 weeks	Primary: Executive function as assessed by D-KEFS measures Secondary: Not reported	Primary: Rivastigmine was associated with significantly more correct responses, fewer set loss errors, and more total responses made (within time available), compared to placebo (all P<0.05). There was no significant difference in total repetition errors (P=0.57). Rivastigmine was associated with a significantly higher Card Sorting recognition description score than placebo (P=0.03). Word reading errors, word comprehension, and sort recognition errors were NS. There were significantly more correct substitutions on the Symbol Digit Modalities Test compared to placebo (P=0.02). Rivastigmine was associated with significantly fewer self-corrected errors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				on the Color-Word Interference inhibition/switching subtest compared to placebo (P=0.049). Treatment differences in numbers of correct responses were near statistical significance (P=0.050). Other treatment differences in this battery of executive function tests were not statistically significant. Secondary: Not reported
Olin et al.[102] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with Parkinson's disease dementia	N=541 24 weeks	Primary: Tolerability and efficacy as measured by ADCS-ADL Secondary: Not reported	Primary: A total of 75.8% of patients completed the study (rivastigmine, 72.7% vs placebo, 82.1%). The primary reasons for discontinuation were adverse events (17.1% for rivastigmine vs 7.8% for placebo) and withdrawal of consent (5.8% rivastigmine vs 1.1% placebo). At 24 weeks, rivastigmine was associated with significantly less deterioration compared to placebo based on ADCS-ADL total scores (-1.1 vs -3.6, respectively; P=0.023). Similar improvement were seen with rivastigmine compared to placebo on the basic ADCS-ADL subscale (-0.5 vs -1.7, respectively; P=0.025), and on high level function ADLs (0.1 vs -1.0; P=0.017). No other measures were significantly different among the treatment groups. Secondary: Not reported
Maidment et al.[103] (2006) 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). 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).

Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double dummy, ER=extended release, HR=hazard ratio, IR=immediate release, ITT=intent to treat, LOCF=last observation carried forward, MA=meta analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=Single-blind, WMD=weighted mean difference
Efficacy Measures Key: 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, CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes, CGA-NPI=Caregiver-Administered Neuropsychiatric Inventory, 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, CMAI-K=Cohen Mansfield Agitation Inventory-Korean type, DAD=Disability Assessment, D-KEFS=Delis-Kaplan Executive Function System, ECG=electrocardiogram, FAB=Frontal Assessment Battery, FAST=Functional Assessment Staging, GBS=Gottfried-Bråne-Steen scale, GDS=Global Deterioration Scale, IADL=Instrumental Activity of Daily Living, IDDD=Interview for Deterioration in Daily Functioning Activities in Dementia, K-MMSE=Korean Mini-Mental Status Exam, MDS-ADL=Minimum Data Set-Activities of Daily Living, MMSE=Mini-Mental Status Exam, M-NCAS=Modified

Nursing Care Assessment Scale, NPI=Neuropsychiatric Inventory, NPI-10=10-item Neuropsychiatric Inventory, QOL=quality of life, QoLS=Quality of Life Scale, PDS=Progressive Deterioration Scale, 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[4-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Parasympathomimetic (Cholinergic Agents)					
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 (creatinine clearance <9 mL/min) and dose titration should be done with caution in moderate impairment.	C	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
Central Nervous System Agents, Miscellaneous					
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

Adverse Drug Events

Table 6. Adverse Drug Events (%)[4-12]

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Cardiovascular				
Angina pectoris	-	-	≥1	-
Atrial fibrillation	≥1	-	≥1	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Bradycardia	≥1	2	≥1	-
Chest pain	1 to 2	≥1	-	-
Heart failure	-	-	≥1	≥1
Hemorrhage	2	-	-	-
Hypertension	1 to 3	-	3	4
Hypotension	≥1	-	≥1	-
Myocardial infarction	-	-	≥1	-
Palpitation	-	-	≥1	-
Peripheral edema	≥1	-	-	≥2
Postural hypotension	-	-	≥1	-
Syncope	2	2	3	≥1
Vasodilation	≥1	-	-	-
Central Nervous System				
Abnormal crying	≥1	-	-	-
Abnormal dreams	3	-	-	-
Aggression	≥1	-	3	≥1
Agitation	-	-	≥1	≥2
Anxiety	-	-	4 to 5; 3*	≥2
Aphasia	≥1	-	-	-
Bradykinesia	-	-	≥1	-
Cerebrovascular accident	-	-	-	≥1
Confusion	2	-	1 to 8	6
Convulsion	≥1	-	≥1	-
Delusions	≥1	-	-	-
Depression	2 to 3	7	1 to 6; 4*	≥2
Dizziness	2 to 8	9	6 to 21; 2 to 7*	7
Dyskinesia	-	-	≥1	-
Emotional lability	2	-	-	-
Fatigue	5	5	4 to 9; 2*	2
Gait abnormality	-	-	≥1	≥2
Hallucination	3	-	4	3
Headache	4 to 10	8	4 to 17; 3 to 4*	6
Hostility	3	-	-	-
Hypokinesia	-	-	-	≥1
Insomnia	5 to 9	5	3 to 9; 1 to 4*	≥2
Irritability	≥1	-	-	-
Malaise	-	≥1	5	-
Nervousness	1 to 3	-	-	-
Paranoid reaction	-	-	≥1	-
Paresthesia	≥1	-	≥1	-
Parkinson's disease worsening	-	-	3	-
Parkinsonism	-	-	2	-
Personality disorder	2	-	-	-
Restlessness	≥1	-	≥1	-
Somnolence	2	4	4 to 5	3
Transient ischemic attack	-	-	≥1	≥1
Tremor	≥1	3	4 to 10; ≥1*	-
Vertigo	≥1	-	≥1; 0 to 2*	≥1

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Dermatological				
Diaphoresis	≥1	-	4	-
Eczema	3	-	-	-
Pruritus	≥1	-	≥1*	-
Rash	≥1	-	≥1	≥1
Skin ulcer	≥1	-	-	-
Urticaria	≥1	-	-	-
Gastrointestinal				
Abdominal pain	≥1	5	4 to 13; 2 to 4*	-
Anorexia	4 to 8	7 to 9	6 to 17; 3 to 9*	≥2
Bloating	≥1	-	-	-
Constipation	≥1	-	5; ≥1*	5
Diarrhea	10	6 to 12	7 to 19; 6 to 10*	≥2
Dyspepsia	≥1	5	1 to 9	-
Epigastric pain	≥1	-	-	-
Eructation	-	-	2	-
Fecal incontinence	≥1	-	≥1	-
Flatulence	-	≥1	4	-
Gastritis	-	-	≥1; ≥1*	-
Gastrointestinal bleeding	≥1	-	-	-
Nausea	6 to 11	13 to 24	29 to 47; 7 to 21*	≥2
Toothache	≥1	-	-	-
Vomiting	5 to 8	6 to 13	17 to 31; 6 to 19*	3
Weight decrease	1 to 3	5 to 7	3; 3 to 8*	≥1
Genitourinary				
Cystitis	≥1	-	-	-
Frequent urination	2	-	-	≥1
Glycosuria	≥1	-	-	-
Hematuria	≥1	3	≥1	-
Libido increased	≥1	-	-	-
Urinary incontinence	2	≥1	≥1*	≥2
Urinary tract infection	≥1	8	7; 2*	≥2
Laboratory Test Abnormalities				
Alkaline phosphatase increased	≥1	-	-	≥1
Creatinine increased	3	-	-	-
Hyperlipemia	2	-	-	-
Hypokalemia	-	-	≥1	-
Lactate dehydrogenase increased	≥1	-	-	-
Musculoskeletal				
Arthralgia	-	-	-	≥2
Arthritis	1 to 2	-	≥1	-
Asthenia	≥1	≥1	2 to 6; 2 to 3*	-
Ataxia	≥1	-	≥1	≥1
Back pain	3	-	≥1	3
Bone fracture	≥1	-	-	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Leg cramps	-	-	≥1	-
Muscle cramps	6	-	-	-
Myalgia	-	-	≥1	-
Rigors	-	-	≥1	-
Respiratory				
Bronchitis	≥1	-	-	≥2
Cough increased	≥1	-	-	4
Dyspnea	≥1	-	≥1	2
Pharyngitis	≥1	-	-	-
Pneumonia	≥1	-	≥1*	≥1
Respiratory tract infection	-	-	-	≥2
Rhinitis	-	4	4	-
Sore Throat	≥1	-	-	-
Special Senses				
Blurred vision	≥1	-	-	-
Cataract	≥1	-	≥1	≥1
Conjunctivitis	-	-	-	≥1
Eye irritation	≥1	-	-	-
Tinnitus	-	-	≥1	-
Other				
Accident	7 to 13	-	-	-
Accidental trauma	-	-	1 to 10	-
Allergy	-	-	≥1	-
Anemia	-	3	≥1; ≥1*	≥1
Dehydration	1 to 2	-	1 to 2; ≥1*	-
Ecchymosis	4 to 5	-	-	-
Edema	≥1	-	≥1	-
Epistaxis	-	-	≥1	-
Fall	-	-	≥1*	≥2
Fever	2	≥1	≥1	-
Flu syndrome	≥1	-	3	≥2
Hot flashes	≥1	-	≥1	-
Infection	1 to 11	-	-	-
Inflicted injury	-	-	-	≥2
Influenza	≥1	-	-	-
Pain	3 to 9	-	-	3

✔ Percent not specified.
- Event not reported or incidence <1%.
*Transdermal patch.

Contraindications

Table 7. Contraindications[4-12]

Contraindications	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
History of application site reaction with rivastigmine transdermal			✔	

Contraindications	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
patch suggestive of allergic contact dermatitis, in the absence of negative allergy testing				
Known hypersensitivity to donepezil hydrochloride or to piperidine derivatives	✔			
Known hypersensitivity to galantamine hydrobromide or any excipients		✔		
Known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation				✔
Known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation			✔	

Warnings/Precautions

Table 8. Warnings/Precautions[4-12]

Warnings/precautions	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Active or occult gastrointestinal bleeding: monitor, especially those with an increased risk for developing ulcers		✔		
All patients should be considered at risk for adverse effects on cardiac conduction, including bradycardia and atrioventricular block, due to vagotonic effects on sinoatrial and atrioventricular nodes		✔		
Application site reactions may occur with the patch form of rivastigmine; discontinue treatment if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and if symptoms do not significantly improve within 48 hours after patch removal			✔	

Warnings/precautions	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Cholinesterase inhibitors are likely to exaggerate succinylcholine type muscle relaxation during anesthesia	✔			
Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block	✔			
Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease	✔	✔		
Cholinomimetics are believed to have some potential to cause generalized convulsions	✔	✔		
Cholinomimetics may cause bladder outflow obstructions	✔	✔		
Conditions that raise urine pH may decrease the urinary elimination of memantine, resulting in increased plasma levels of memantine				✔
Gastrointestinal adverse reactions; may include significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss, and may necessitate treatment interruption; dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes			✔	
Hospitalization and, rarely, death have been reported due to application of multiple patches at same time; ensure patients or caregivers receive instruction on proper dosing and administration			✔	
Hypersensitivity reactions of the skin; discontinue rivastigmine in case of disseminated hypersensitivity reaction of the skin, which may occur after oral or transdermal administration			✔	
In patients with suspected allergic contact dermatitis after transdermal rivastigmine use, switch to oral rivastigmine only			✔	

Warnings/precautions	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
after negative allergy testing				
May cause vomiting, patients should be observed closely at initiation of treatment and after dose increases	✔			
Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers	✔			
Use in a dose of 23 mg once daily is associated with weight loss	✔			

Drug Interactions

There are no significant drug interactions reported with the Alzheimer's agents.[4]

Dosage and Administration

Table 9. Dosing and Administration[4-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic Agents)			
Donepezil	Dementia of the Alzheimer's type (mild to moderate): 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 Dementia of the Alzheimer's type (moderate to severe): Tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; may increase to 23 mg 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	Safety and efficacy not established in the pediatric population.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg
Galantamine	Mild-to-moderate dementia of the Alzheimer's type: Extended-release capsule: initial, 8 mg daily; maintenance, 16 to 24 mg daily Tablet and oral solution: initial,	Safety and efficacy not established in the pediatric population.	Extended release capsule: 8 mg 16 mg 24 mg Solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	4 mg twice a day with the morning and evening meals; maintenance: 8 to 12 mg twice a daily		4 mg/mL Tablet: 4 mg 8 mg 12 mg
Rivastigmine	Mild-to-moderate dementia of the Alzheimer's type: 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 or 13.3 mg/24 hours Severe dementia of the Alzheimer's type: Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 13.3 mg/24 hours Mild-to-moderate dementia associated with Parkinson's disease: 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 or 13.3 mg/24 hours	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
Central Nervous System Agents, Miscellaneous			
Memantine	Moderate-to-severe dementia of the Alzheimer's type: Solution and tablet: initial, 5 mg once daily, increase dose by 5 mg at weekly intervals (twice daily dosing); maintenance, 10 mg twice daily Extended release capsule: initial, 7 mg once daily; maintenance, 28 mg once daily	Safety and efficacy not established in the pediatric population.	Extended release capsule: 7 mg 14 mg 21 mg 28 mg Solution: 10 mg/5 mL Tablet: 5 mg 10 mg

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies: **Guidelines for the Diagnosis and Management of Alzheimer's Disease (2010)**[104]	• Patients and caregivers should be provided with education and support. • There is insufficient evidence to support the use of any drugs purely for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and oestrogens should not be used as treatments for those with mild cognitive impairment. • In patients with Alzheimer's disease, treatment with cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • In patients with moderate to severe Alzheimer's disease, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and noncognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • Regular patient follow-up should be an integral part of management. • Aspirin should not be used as a treatment for Alzheimer's disease, though it can be used in those with Alzheimer's disease who also have other indications for its use (e.g. to prevent cardiovascular events). • Vitamin E should not be used as a treatment for Alzheimer's disease. • Currently, there is insufficient evidence to support the use of other agents including, anti-inflammatory drugs, nootropics (including piracetam, nicergoline), selegiline, oestrogens, pentoxyphylin, or statins in the treatment or prevention of Alzheimer's disease. • Cognitive stimulation or rehabilitation may be considered in patients with mild to moderate Alzheimer's disease. • Management of behavioral and psychological symptoms of dementia should begin with a careful search for triggers and causative factors (i.e. physical illness). Where possible, initial treatment should be non-pharmacological. • Antipsychotics should only be used for moderate or severe behavioral and psychological symptoms of dementia causing significant distress which have either not responded to other treatments (like non-pharmacological measures or cholinesterase inhibitors) or when other treatments are not appropriate. Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver. • Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs. • Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in Alzheimer's disease.
American College of Physicians/ American Academy of Family Physicians: **Current**	• The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. • Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of

Clinical Guideline	Recommendation(s)
Pharmacologic Treatment of Dementia: A Clinical Practice Guideline (2008)[105]	dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. Currently, there is no way to predict which patients might have a clinically important response. The evidence does not support prescribing these medications for every patient with dementia. • Evidence is insufficient to determine the optimal duration of therapy. No evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. If slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate. • The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Assessment of the effectiveness of combination therapy is lacking. • Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile and ease of use.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and other Dementias (2007)[106]**	• The primary goal of medication treatment for cognitive symptoms in dementia is to delay the progression of symptoms, with the hope that this delay will translate into a preservation of functional ability, maintaining the patient for as long as possible at a particular level of symptom severity. However, no medication treatment has been shown to delay the progression of neurodegeneration. • Given the evidence from randomized controlled trials for modest improvement in some patients treated with cholinesterase inhibitors and the lack of established alternatives, it is appropriate to offer a trial of one of these agents for patients with mild or moderate Alzheimer's disease for whom the medication is not contraindicated. • Results of the numerous large placebo-controlled trials of individual cholinesterase inhibitors have suggested similar degrees of efficacy, although tolerability may differ among the medications. Currently available data do not allow a fair, unbiased direct comparison among the cholinesterase inhibitors. There is also no data on whether or how to switch from one cholinesterase inhibitor to another. • Reversible, direct medication-induced hepatotoxicity with hepatocellular injury is a unique property of tacrine. Because of this hepatotoxicity, tacrine is very uncommonly used. Hepatotoxicity has not been associated with donepezil, rivastigmine, or galantamine. • Donepezil, rivastigmine and galantamine are preferred over tacrine because of reversible hepatic toxicity and the requirement that it be given four times per day. • It is uncertain how long patients should be treated with cholinesterase inhibitors. The decision whether to continue treatment with cholinesterase inhibitors is highly individualized. Reasons that patients choose to stop taking these medications include side effects, adverse events, lack of motivation and lack of perceived efficacy. • Memantine should be considered for the treatment of patients with moderate to severe Alzheimer's disease. Memantine can be prescribed for people either currently taking or not taking a cholinesterase inhibitor. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine alone.

Clinical Guideline	Recommendation(s)
	• Vitamin E (α-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns. • Nonsteroidal anti-inflammatory agents, statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's disease and therefore are not recommended. • Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. Only rivastigmine has been approved by the Food and Drug Administration for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor. Dosing and titration are similar to those for patients with Alzheimer's disease.
American Academy of Neurology: **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2001; reaffirmed 2003)**[107]	<u>Pharmacologic treatment of Alzheimer's disease</u> • Cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, 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 Alzheimer's disease. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatory or other putative disease-modifying agents specifically to treat Alzheimer's disease because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat Alzheimer's disease. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. <u>Pharmacologic treatment for noncognitive symptoms of dementia</u> • 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 (e.g., 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. <u>Educational Interventions for patients with dementia and/or caregivers</u> • Short-term programs directed toward educating family caregivers about Alzheimer's disease should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with Alzheimer's disease to delay time to nursing home placement. • Staff of long-term care facilities should receive education about Alzheimer's disease 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 behaviors, problem behaviors, and care environment alterations.
American Academy of Neurology: **Practice Parameter: Evaluation and Treatment of**	• For patients with Parkinson's disease dementia or dementia with Lewy bodies, rivastigmine is probably effective in improving cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated. • For patients with Parkinson's disease dementia, donepezil is probably effective in improving cognitive function. However, the magnitude of the

Clinical Guideline	Recommendation(s)
Depression, Psychosis, and Dementia in Parkinson Disease (2006)[108]	benefits is modest. Donepezil should be considered for the treatment of dementia in Parkinson's disease.

Conclusions

The cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease. Donepezil is also approved for the treatment of severe disease. The N-Methyl-D-aspartate (NMDA) receptor antagonist, memantine, has only been approved for the treatment of moderate-to-severe Alzheimer's disease. Although these agents provide symptomatic benefit, they have not been shown to delay the progression of neurodegeneration. Donepezil, galantamine and rivastigmine are available in a generic formulation.

There are several guidelines which discuss the role of these agents in the management of Alzheimer's disease.[104-108] The primary goal of treatment is to delay the progression of symptoms and preserve functional ability.[106] The use of a cholinesterase inhibitor may lead to modest improvements in some patients; therefore, it is appropriate to offer a trial of one of these agents for patients with mild-to-moderate disease.[105-106] Memantine can be considered for the treatment of patients with moderate-to-severe disease and it may be prescribed as monotherapy or in combination with a cholinesterase inhibitor.[106] Guidelines do not give preference to one agent over another. Clinicians should base the treatment decision on tolerability, adverse events and ease of use.[105]

Numerous clinical trials have evaluated the efficacy and safety of the cholinesterase inhibitors and memantine. Several outcomes have been assessed (using more than 40 different instruments), including cognition, global function, behavior and quality of life. There is consistent evidence from well-designed studies that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. The findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of these clinical trials were less than one year. Thus, there is insufficient evidence to determine the optimal duration of therapy.[105-106] There are relatively few studies that directly compare the efficacy and safety of the Alzheimer's agents. Most of the trials have compared active treatment to placebo or no treatment. The studies also differ with regards to design, patient population and treatment duration, which make it difficult to compare the results.

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

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