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 8 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 five agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine), an NMDA receptor antagonist (memantine) and a combination product (memantine extended release [ER]/donepezil).[4-13] 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. Currently, memantine ER (Namenda XR®) and memantine ER/donepezil (Namzaric®) are the only products not available generically.

Table 1. Medications Included Within the Therapeutic Class Review[4-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Products			
Donepezil* (Aricept®*)	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 Tablet: 4 mg 8 mg 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	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	patch) Mild-to-moderate dementia associated with Parkinson's disease	Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours	
Memantine (Namenda®*, Namenda XR®, Namenda Titration Pack®*, Namenda XR Titration Pack®)	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	✔
Combination Products			
Memantine ER/donepezil (Namzaric®)	Moderate to severe dementia of the Alzheimer's type for patients stabilized on memantine and donepezil	Capsule: 14 mg/10 mg 28 mg/10 mg	-

ER=extended-release
*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.[15-103]
- 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.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[104-109]
    - 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.
    - Evidence does not show clinically meaningful advantages to administering higher doses of donepezil; however, higher doses of rivastigmine patch may be associated with greater benefit.[107]
- Other Key Facts:
    - Memantine ER (Namenda XR®) and memantine ER/donepezil (Namzaric®) are the only products not available generically.

- Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
2. Grabowski T. Clinical manifestations and diagnosis of Alzheimer disease. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2014.
3. Press D, Alexander M. Treatment of dementia. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2014.
4. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2014. Available from Wolters Kluwer Health, Inc. Accessed February 2014.
5. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2014; February 2014.
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 2014.
7. Aricept®, Aricept ODT®[package insert]. Woodcliff Lake, NJ: Eisai, Inc.; July 2015.
8. Razadyne® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; December 2015.
9. Exelon® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2015.
10. Exelon® Patch [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2015.
11. Namenda® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; October 2013.
12. Namenda XR® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; September 2014.
13. Namzaric® [package insert]. Cincinnati, OH: Forest Laboratories, LLC; February 2015.
14. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc. 2003 Jul;51(7):937-44.
15. Burns A, Gauthier S, Perdomo C, et al. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2007;22:806-12.
16. Hashimoto M, Yatabe Y, Kaneda K, et al. Impact of donepezil hydrochloride on the care burden of family caregivers of patients with Alzheimer's disease. Psychogeriatrics. 2009;9:196-203.
17. Homma A, Imai Y, Tago H, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement Geriatr Cogn Disord. 2009;27:232-9.
18. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15.
19. Sabbagh M. Cummings J. Christensen D. Doody R. Farlow M. Liu L. Mackell J. Fain R. Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response. BMC Geriatrics. 2013;13:56.
20. Tariot P. Salloway S. Yardley J. Mackell J. Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. BMC Research Notes. 2012;5:283.
21. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21(5-6):353-63.
22. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology. 1998 Jan;50(1):136-45.
23. Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL Jansson-Blixt C, et al; Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.
24. Black SE, Doody R, Li H, McRae T, Jambor KM, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology. 2007;69:459-69.
25. Homma A, Imai Y, Tago H, et al. Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. Dement Geriatr Cogn Disord. 2008;25:399-407.
26. Birks J, Harvey RD. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001190. doi: doi: 10.1002/14651858.CD001190.pub2.
27. Wallin A et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dementia and Geriatric Cognitive Disorders. 2007;23:150-60.
28. Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) vs standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Clin Ther. 2010;32:1234-51.
29. Ferris SH, Schmitt FA, Saxton J, et al. Analyzing the impact of 23 mg/day donepezil on language dysfunction in moderate to severe Alzheimer's disease. Alzheimers Res Ther. 2011;3:22.
30. Farlow M, Veloso F, Moline M, et al. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. BMC Neurol. 2011;11:57.
31. Doody RS. Geldmacher DS. Farlow MR. Sun Y. Moline M. Mackell J. Efficacy and safety of donepezil 23 mg vs donepezil 10 mg for moderate-to-severe Alzheimer's disease: a subgroup analysis in patients already taking or not taking concomitant memantine. Dementia & Geriatric Cognitive Disorders. 2012;3(2-3):164-73.
32. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
33. Rockwood K, Dai D, Mitnitski A, et al. Patterns of decline and evidence of subgroups in patients with Alzheimer's disease taking galantamine for up to 48 months. Int J Geriatr Psychiatry. 2008;23:207-14.
34. Wallin AK, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. Neuropsychiatr Dis Treat. 2011;7:565-76.

35. Brodaty H et al. A Naturalistic Study of Galantamine for Alzheimer's disease. CNS Drugs. 2006;20(11):935-46.
36. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry. 2004 Mar;161(3):532-8.
37. Scarpini E, Bruno G, Zappalà G, et al. Cessation vs continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J Alzheimers Dis. 2011;26:211-20.
38. Kavanagh S, Howe I, Brashear HR, et al. Long-term response to galantamine in relation to short-term efficacy data: pooled analysis in patients with mild to moderate Alzheimer's disease. Curr Alzheimer Res. 2011;8:175-86.
39. Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol. 2009;8:39-47.
40. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
41. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9.
42. Dunbar F, Zhu Y, Brashear H. Post hoc comparison of daily rates of nausea and vomiting with once- and twice-daily galantamine from a double-blind, placebo-controlled, parallel-group, 6-month study. Clin Ther. 2006 Mar;28(3):365-72.
43. Brodaty H, Corey-Bloom J, Potocnik F, Truyen L, Gold M, et al. Galantamine prolonged-release formulation in the treatment of mild-to-moderate Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2005;20:120-32.
44. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006, Issue 1.Art.No.:CD001747. DOI: 10.1002/14651858.CD001747.pub3.
45. Herrmann N, Cappell J, Eryavec GM, Lanctôt KL. Changes in nursing burden following memantine for agitation and aggression in long-term care residents with moderate to severe Alzheimer's disease: an open-label pilot study. CNS Drugs. 2011;25:425-33.
46. Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis. 2007;11:471-9.
47. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41.
48. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry. 1999;14(2):135-46.
49. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord. 2007;24(1):20-7.
50. Wilkinson D and Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate-to-severe Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2007;24:138-45.
51. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database of Systematic Reviews 2006, Issue 2.Art.No.:CD003154. DOI: 10.1002/14651858.CD003154.pub5.
52. Grossberg GT. Manes F. Allegri RF. Gutierrez-Robledo LM. Gloger S. Xie L. Jia XD. Pejovic V. Miller ML. Perhach JL. Graham SM. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs. 2013 Jun;27(6):469-78.
53. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Mar;19(3):243-9
54. Dantoine T, Auriacombe S, Sarazin M, et al. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. International Journal of Clinical Practice. 2006;60(1):110-8.
55. Olin JT, Bhatnagar V, Reyes P, et al. Safety and tolerability of rivastigmine capsule with memantine in patients with probable Alzheimer's disease: a 26-week, open-label, prospective trial (Study ENA713B US32). Int J Geriatr Psychiatry. 2010;25:419-26.
56. Gauthier S, Juby A, Dalziel W, Réhel B, Schecter R; EXPLORE investigators. Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). Curr Med Res Opin. 2010;26:1149-60.
57. Birks J, Grimely EJ, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2000, Issue 4. Art. No.: CD001191. DOI: 10.1002/14651858.CD001191.
58. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2009; (2); Cochrane AN: CD001191.
59. Rosler M, Anand R, Cicin-Sain A, Gauthier S, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomized controlled trial. BMJ. 1999;318:633-40.
60. Articus K, Baier M, Tracik F, et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. Int J Clin Pract. 2011;65:790-6.
61. Grossberg G, Sadowsky C, Fröstl H, et al. Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension. Alzheimer Dis Assoc Disord. 2009;23:158-64.
62. Gauthier S. Robillard A. Cohen S. Black S. Sampalis J. Colizza D. de Takacsy F. Schecter R. EMBRACE investigators. Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study. Current Medical Research & Opinion. 2013 Aug;29(8):989-1000.
63. Sadowsky CH, Farlow MR, Meng X, Olin JT. Safety and tolerability of rivastigmine transdermal patch compared to rivastigmine capsules in patients switched from donepezil: data from three clinical trials. Int J Clin Pract. 2010;64:188-93.
64. Cummings J, Froelich L, Black SE, Bakchine S, Bellelli G, Molinuevo JL,et al. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm²) in Alzheimer's disease. Dement Geriatr CognDisord. 2012;33(5):341-53.

65. Cummings JL, Farlow MR, Meng X, et al. Rivastigmine transdermal patch skin tolerability: results of a 1-year clinical trial in patients with mild-to-moderate Alzheimer's disease. Clin Drug Investig. 2010;30:41-9.
66. Molinuevo JL, Arranz FJ. Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. Expert Rev Neurother. 2012;12:31-7.
67. Boada M. Arranz FJ. Transdermal is better than oral: observational research of the satisfaction of caregivers of patients with Alzheimer's disease treated with rivastigmine. Dementia & Geriatric Cognitive Disorders. 2013;35(1-2):23-33.
68. Blesa González R, Boada Rovira M, Martínez Parra C, et al. Evaluation of the convenience of changing the rivastigmine administration route in patients with Alzheimer disease. Neurologia. 2011;26:262-71.
69. Winblad B, Grossberg G, Frolich L, Farlow M, et al. IDEAL: a 6 month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69(Suppl1):S14-S22.
70. Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. Int J Geriatr Psychiatry. 2007 May;22(5):485-91.
71. Winblad B, Cummings J, Andreasen N, Grossberg G, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-rivastigmine patch vs capsule. International Journal of Geriatric Psychiatry. 2007;22:456-67.
72. Blesa R, et al. Caregiver preference for rivastigmine patches vs capsules for the treatment of Alzheimer disease. Neurology. 2007;69(Suppl 1):S23-S28.
73. Farlow MR, Grossberg GT, Meng X, et al. Rivastigmine transdermal patch and capsule in Alzheimer's disease: influence of disease stage on response to therapy. Int J Geriatr Psychiatry. 2011 Dec;26(12):1236-43.
74. Choi SH, Park KW, Na DL, et al.; Expect Study Group. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. Curr Med Res Opin. 2011;27:1375-83.
75. Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. Curr Med Res Opin. 2010;26:263-9.
76. Harry RD, Zakzanis KK. A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis. Hum Psychopharmacol.. 2005 Apr;20(3):183-7.
77. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P; GAL-GBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging. 2003;20(10):777-89.
78. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild-to-moderate Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Jan;19(1):58-67.
79. Modrego PJ, Fayed N, Errea JM, et al. Memantine vs donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. Eur J Neurol. 2010;17:405-12.
80. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild-to-moderate Alzheimer's disease. Int J Clin Pract. 2002;56(6):441-6.
81. Van Puyvelde K, Mets T; RODOS Study Group. Galantamine (Reminyl) once daily outcome and satisfaction survey (RODOS) in mild to moderate Alzheimer's disease: a study in a real life population. Geriatr Gerontol Int. 2011;11:256-61.
82. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate-to-severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004 Jan 21;291(3):317-24.
83. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin. 2005;21:1317-1327.
84. Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, Bencini F, Mecacci R, Marini M, Bardelli F, Sarcone E, Razzi E, Biagini CA, Masotti G. Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. Arch Gerontol Geriatr Suppl. 2004;(9):297-307.
85. Aguglia E, Onor ML, Saina M, Maso E. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. Curr Med Res Opin. 2004 Nov;20(11):1747-52.
86. Lopez-Pousa S, Turon-Estrada A, Garre-Olmo J, Pericot-Nierga I, Lozano-Gallego M, Vilalta-Franch M, Hernandez-Ferrandiz M, Morante-Munoz V, Isern-Vila A, Gelada-Batlle E, Majo-Llopart J. Differential efficacy of treatment with acetylcholinesterase inhibitors in patients with mild and moderate Alzheimer's disease over a 6-month period. Dement Geriatr Cogn Disord. 2005;19(4):189-95.
87. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr 2009;21:813-24.
88. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012;366:893-903.
89. Porsteinsson AP, Grossberg GT, Mintzer J, et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res. 2008;5:83-9.
90. Cumming JL, Schneider E, Tariot P, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology. 2006;67:57-63.
91. Maidment ID, Fox CG, Boustani M, et al. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. Ann Pharmacother. 2008;42:32-8.
92. Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease. Dement Geriatr Cogn Disord. 2009;28:244-51.

93. Feldman HH, Pirttila T, Dartigues JF, et al. Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. Int J Geriatr Psychiatry. 2009;24:479-88.
94. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. JAMA. 2003 Jan 8;289(2):210-6.
95. Lanctôt K, Herrmann N, Yau K, Khan L, Liu B et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ. 2003 Sept 16;(6) 2003;169.
96. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006, Issue1.Art.No.:CD005593.DOI: 10.1002/14651858.CD005593.
97. Hansen RA, Gartlehner G, Webb AP, et al. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008;3:211-25.
98. Kim DH, Brown RT, Ding EL, et al. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc. 2011 Jun;59(6):1019-31.
99. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. NEJM. 2004;351(24):2509-18.
100. Wesnes KA, McKeith I, Edgar C, Emre M, Lane R. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology. 2005;65:1654-6.
101. Schmitt FA, Farlow MR, Meng X, et al. Efficacy of rivastigmine on executive function in patients with Parkinson's disease dementia. CNS Neurosci Ther 2010;16:330-6.
102. Olin JT, Aarsland D, Meng X. Rivastigmine in the treatment of dementia associated with Parkinson's disease: effects on activities of daily living. Dement Geriatr Cogn Disord. 2010;29(6):510-5.
103. Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. Cochrane Database Syst Rev. 2006, Issue 1.Art. No.: CD004747. DOI: 10.1002/14651858.CD004747.pub2.
104. Hort J, O'Brien JT, Gainotti G, et al. EFNS Scientist Panel on Dementia. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol. 2010;17(10):1236–48.
105. Qaseem A, Snow V, Cross J, et al. American College of Physicians/American Academy of Family Physicians Panel on Dementia. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2008;148:370-8.
106. American Psychiatric Association (APA). Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Arlington (VA): American Psychiatric Association (APA); 2007.
107. Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Guideline Watch (October 2014): Practice Guideline For The Treatment Of Patients With Alzheimer's Disease and Other Dementias. Arlington (VA): American Psychiatric Association (APA): 2014.
108. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001 May 8;56(9):1154-66 [reaffirmed October 2003].
109. Miyasaki JM, Shannon K, Voon V, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:996-1002.