

Data supplement

Table DS1 Summary of cardiovascular adverse effects documented in double-blind, randomised, placebo-controlled, parallel-group trials of acetylcholinesterase inhibitors for Alzheimer's disease

Drug	Reference	Sample size, n	Participants who experienced adverse effects (%; drug v. placebo)	Serious adverse effects in drug group	Adverse effect related to drug?
Donepezil	Homma <i>et al</i> , 2000	268	Nil	Nil	
Donepezil	Rogers <i>et al</i> , 1996	161	Dizziness (8 v. 10)	Nil	
Donepezil	Burns <i>et al</i> , 1999	818	Dizziness (9 v. 5) in 10 mg/day group	Nil	
Donepezil	Tariot <i>et al</i> , 2001	208	Dizziness (8 v. 8) Bradycardia (6 v. 5)	Death due to congestive cardiac failure (n=1)	Not related
Donepezil	Anonymous, 2004	565	Not commented on	Nil	
Donepezil	Rogers <i>et al</i> , 1998	473	Dizziness (9 v. 4)	Angina (n=1) Syncope (n=2)	Not related 1 possibly related
Donepezil	Mohs <i>et al</i> , 2001	431	Nil	Syncope (n=3)	Possibly related
Donepezil	Feldman <i>et al</i> , 2001	473	Dizziness (6.3 v. 4.8) Bradycardia (1.4 v. 0)	Death due to myocardial infarction (n=1)	Not related
Donepezil	Greenberg <i>et al</i> , 2000	60	Nil	Syncope (n=1) Seizure (n=1)	Possibly related Possibly related
Donepezil	Seltzer <i>et al</i> , 2004	153	Dizziness (8 v. 2)	Syncope (n=1) Dizziness (n=1)	Not related Not related
Donepezil	Salloway <i>et al</i> , 2004	270	Nil	Atrial fibrillation (n=1)	Possibly related
Donepezil	Winblad <i>et al</i> , 2001	286	Dizziness (6.3 v. 4.2) Syncope (6.3 v. 2.8) Sinus bradycardia (9.2 v. 6.9; NS)	Syncope (n=3)	Not related
Donepezil	Black <i>et al</i> , 2003 Vascular dementia	603	Sinus bradycardia (3.5 v. 2.5; NS) Syncope (3 v. 1.5; NS)	Nil	
Galantamine	Wilkinson & Murray, 2001	285	Dizziness (7.4 v. 3.4) with high dose	Causes not described	
Galantamine	Wilcock <i>et al</i> , 2000	653	Dizziness (11.4 v. 5) with high dose	Causes not described	
Galantamine	Rockwood <i>et al</i> , 2001	386	Dizziness (14.9 v. 4)	Causes not described	
Galantamine	Tariot <i>et al</i> , 2000	978	Nil	Causes not described	
Galantamine	Raskind <i>et al</i> , 2000	636	Dizziness (16 v. 11)	Causes not described	
Rivastigmine	Rosler <i>et al</i> , 1999	725	Dizziness (high dose: 20 v. 7; low dose: 10 v. 7)	Causes not described	
Rivastigmine	Corey-Bloom <i>et al</i> , 1998	699	Titration phase: dizziness (high dose: 24 v. 13; low dose: 15 v. 13) Maintenance phase: dizziness (high dose: 14 v. 4; low dose: 8 v. 4)	Causes not described	

Table DS2 Summary of cardiovascular adverse effects found in studies of acetylcholinesterase inhibitors¹

Drug	Study	Sample size, n	Adverse effects (% of participants)	Serious adverse effect	Adverse effect related to drug?
Donepezil	Froelich <i>et al</i> , 2004	237	Bradycardia (2.5) Tachycardia (1.3) Postural hypotension (4.6) Hypertension (4.7)	Syncope (n=4, 1.7%)	Not related
Donepezil	Rogers & Friedhoff, 1998	133	Dizziness (14)	Syncope (n=2) Seizure (n=2) Atrial arrhythmia (n=1)	Possibly related Not related Not related
Donepezil	Rogers <i>et al</i> , 2000	133	Dizziness (7)	Death due to myocardial infarction (n=2)	Not related
Galantamine	Pirttila <i>et al</i> , 2004	363	Dizziness (8.4) Falls (11.2) – cause not specified	Nil	
Galantamine	Lyketsos <i>et al</i> , 2004	699	Dizziness (10.9)	Syncope (n=16, 2.3%)	No comment
Galantamine	Kurz <i>et al</i> , 2003	326	Bradycardia (3) Syncope (3)	Myocardial infarction (n=2)	No comment
Rivastigmine	Grossberg <i>et al</i> , 2004	2010	Dizziness (13.5)	Nil	
Donepezil, galantamine, rivastigmine	Mossello <i>et al</i> , 2004 (real-world study)	407		n=1 with rivastigmine – no details given	
Donepezil, galantamine, rivastigmine	Aguglia <i>et al</i> , 2004	242		2% – no details given	
Donepezil Rivastigmine	Wilkinson <i>et al</i> , 2002	111	Bradycardia at 51–58 bpm: donepezil (3.6) rivastigmine (5.5)	Nil	

1. All studies were open-label, unless otherwise indicated.

References

- Aguglia, E., Onor, M. L., Saina, M., *et al* (2004) An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. *Current Medical Research and Opinion*, **20**, 1747–1753.
- Anonymous (2004) Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*, **363**, 2105–2116.
- Black, S., Roman, G. C. & Geldmacher, D. S. (2003) Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*, **34**, 2331–2332.
- Burns, A., Rossor, M., Hecker, J., *et al* (1999) The effects of donepezil in Alzheimer's disease – results from a multinational trial. *Dementia and Geriatric Cognitive Disorders*, **10**, 237–244.
- Corey-Bloom, J., Anand, R. & Veach, J. (1998) A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *International Journal of Geriatric Psychopharmacology*, **1**, 55–65.
- Feldman, H., Gauthier, S., Hecker, J., *et al* (2001) A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*, **57**, 613–620.
- Froelich, L., Gertz, H. J., Heun, R., *et al* (2004) Donepezil for Alzheimer's disease in clinical practice – The DONALD Study. *Dementia and Geriatric Cognitive Disorders*, **18**, 37–43.
- Greenberg, S. M., Tennis, M. K., Brown, L. B., *et al* (2000) Donepezil therapy in clinical practice: a randomised crossover study. *Archives of Neurology*, **57**, 94–99.
- Grossberg, G., Irwin, P., Satlin, A., *et al* (2004) Rivastigmine in Alzheimer disease: efficacy over two years. *American Journal of Geriatric Psychiatry*, **12**, 420–431.
- Homma, A., Takeda, M., Imai, Y., *et al* (2000) Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease: a 24-week, multicenter, double-blind, placebo controlled study in Japan. *Dementia and Geriatric Cognitive Disorders*, **11**, 299–313.
- Kurz, A. F., Erkinjuntti, T., Small, G. W., *et al* (2003) Long-term safety and cognitive effects of galantamine in the treatment of probable vascular dementia or Alzheimer's disease with cerebrovascular disease. *European Journal of Neurology*, **10**, 633.
- Lyketsos, C. G., Reichman, W. E., Kershaw, P., *et al* (2004) Long-term outcomes of galantamine treatment in patients with Alzheimer disease. *American Journal of Geriatric Psychiatry*, **12**, 473–483.

- Mohs, R. C., Doody, R. S., Morris, J. C., *et al* (2001) A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*, **57**, 481–488.
- Mossello, E., Tonon, E., Caleri, V., *et al* (2004) Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. *Archives of Gerontology and Geriatrics*, **9**, 297–307.
- Pirttila, T., Wilcock, G., Truyen, L., *et al* (2004) Long-term efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicenter trial. *European Journal of Neurology*, **11**, 734–741.
- Raskind, M. A., Peskind, E. R., Wessel, T., *et al* (2000) Galantamine in AD: a 6-month, randomized, placebo-controlled trial with a 6-month extension. *Neurology*, **54**, 2261–2268.
- Rockwood, K., Mintzer, J., Truyen, L., *et al* (2001) Effects of a flexible galantamine dose in Alzheimer's disease: a randomized controlled trial. *Journal of Neurology, Neurosurgery and Psychiatry*, **71**, 589–595.
- Rogers, S. L. & Friedhoff, L. T. (1998) Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *European Neuropsychopharmacology*, **8**, 67–75.
- Rogers, S. L., Friedhoff, L. T. and the Donepezil Study Group (1996) The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomised, double-blind, placebo-controlled trial. *Dementia*, **7**, 293–303.
- Rogers, S. L., Farlow, M. R., Doody, R. S., *et al* (1998) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*, **50**, 136–145.
- Rogers, S. L., Doody, R. S., Pratt, R. D., *et al* (2000) Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open label study. *European Neuropsychopharmacology*, **10**, 195–203.
- Rosler, M., Anand, R., Cicin-Aain, A., *et al* (1999) Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ*, **318**, 633–638.
- Salloway, S., Ferris, S., Kluger, A., *et al* (2004) Efficacy of donepezil in mild cognitive impairment – a randomized placebo-controlled trial. *Neurology*, **63**, 651–657.
- Seltzer, B., Zolnounio, P., Nunez, M., *et al* (2004) Efficacy of donepezil in early-stage Alzheimer's disease – a randomized placebo-controlled trial. *Archives of Neurology*, **61**, 1852–1856.
- Tariot, P. N., Solomon, P. R., Morris, J. C., *et al* (2000) A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology*, **54**, 2269–2276.
- Tariot, P. N., Cummings, J. L., Katz, I. R., *et al* (2001) A randomised, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *Journal of the American Geriatric Society*, **49**, 1590–1599.
- Wilcock, G. K., Lilienfeld, S. & Gaens, E. (2000) Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ*, **321**, 1445–1449.
- Wilkinson, D. & Murray, J. (2001) Galantamine: a randomized double-blind dose comparison in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, **16**, 852–857.
- Wilkinson, D. G., Passmore, A. P., Bullock, R., *et al* (2002) A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *International Journal of Clinical Practice*, **56**, 441–446.
- Winblad, B., Engedal, K., Soininen, H., *et al* (2001) A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*, **57**, 489–495.