

Appendix Table 4. Summary Estimates of Adverse Events*

Number of Studies (Reference)	Adverse Events	Consistency of Effects	Total Number of Patients (%)		Magnitude of Effect (95% CI)	Limitations of Studies
			Drug [min, max %]	Placebo [min, max %]		
Donepezil						
Donepezil vs. placebo (Alzheimer's disease)						
3 (13, 14, 16)	Abdominal Pain	Moderate inconsistency (I ² = 49.5%)	22/389 (5.7%) [2.1, 9.7]	23/395 (5.8%) [4.8, 6.8]	RR: 0.95 (0.40, 2.25)	Some limitations
8 (10, 13-16, 18, 19, 33)	Accidental Injury	No important inconsistency (I ² = 0.0%)	125/1024 (12.2%) [5.5, 65.0]	101/982 (10.3%) [0.0, 55.2]	RR: 1.19 (0.98, 1.44)	Some limitations
4 (15, 18, 19, 12)	Agitation	No important inconsistency (I ² = 0.0%)	42/427 (9.8%) [2.6, 18.8]	34/424 (8.0%) [0.0, 9.7]	RR: 1.20 (0.78, 1.86)	Some limitations
6 (9, 12, 15-18,)	Anorexia	No important inconsistency (I ² = 0.0%)	67/921 (7.3%) [5.6, 18.8]	19/925 (2.1%) [0.0, 4.8]	RR: 3.21 (1.94, 5.33)	Some limitations
2 (13, 33)	Anxiety	High inconsistency (I ² = 55.4%)	23/270 (8.5%) [6.3, 10.6]	18/264 (6.8%) [5.6, 8.3]	RR: 1.21 (0.49, 3.02)	Some limitations
2 (14, 16)	Arthralgia	High inconsistency (I ² = 82.5%)	20/247 (8.1%) [6.9, 14.3]	17/251 (6.8%) [1.4, 14.3]	RR: 1.67 (0.23, 12.32)	Some limitations
6 (10, 13-16, 33)	Asthenia	No important inconsistency (I ² = 2.0%)	65/827 (7.9%) [3.1, 13.6]	37/789 (4.7%) [1.8, 8.6]	RR: 1.65 (1.09, 2.48)	Some limitations
2 (14, 16)	Back pain	No important inconsistency (I ² = 0.0%)	24/247 (9.7%) [7.6, 12.6]	15/251 (6.0%) [4.8, 7.6]	RR: 1.63 (0.88, 3.02)	Some limitations
2 (18, 19)	Common cold	No important inconsistency (I ² = 0.0%)	9/197 (4.6%) [4.4, 5.1]	12/193 (6.2%) [5.0, 6.5]	RR: 0.74 (0.32, 1.71)	Some limitations
4 (9, 13, 14, 16)	Confusion	No important inconsistency (I ² = 0.0%)	35/662 (5.3%) [2.8, 6.3]	42/669 (6.3%) [5.5, 8.6]	RR: 0.85 (0.55, 1.32)	Some limitations
3 (13, 19, 33)	Constipation	No important inconsistency (I ² = 0.0%)	14/309 (4.5%) [3.9, 7.7]	16/304 (5.3%) [2.5, 6.3]	RR: 0.84 (0.41, 1.72)	Some limitations
3 (16, 18, 19)	Cough	Moderate inconsistency (I ² = 25.7%)	21/300 (7.0%) [1.9, 16.5]	25/298 (8.4%) [5.0, 14.3]	RR: 0.78 (0.36, 1.71)	Some limitations
2 (13, 14)	Depression	No important	24/286 (8.4%)	16/290 (5.5%)	RR: 1.52	Some

		inconsistency (I ² = 0.0%)	[5.6, 11.3]	[3.4, 7.6]	(0.83, 2.79)	limitations
11 (9, 10, 12-20, 33)	Diarrhea	No important inconsistency (I ² = 15.6%)	213/1470 (14.5%) [7.0, 37.5]	76/1432 (5.3%) [2.5, 21.4]	RR: 2.57 (1.93, 3.41)	Some limitations
9 (9, 10, 12, 13, 14, 16-, 19)	Dizziness	No important inconsistency (I ² = 0.0%)	91/1128 (8.1%) [6.3, 12.5]	59/1095 (5.4%) [1.8, 14.3]	RR: 1.47 (1.06, 2.03)	Some limitations
3 (12, 17, 18)	Fatigue	No important inconsistency (I ² = 4.4%)	31/331 (9.4%) [7.6, 43.8]	13/329 (4.0%) [1.9, 14.3]	RR: 2.24 (1.17, 4.30)	Some limitations
3 (18, 19, 33)	Gastric or stomach upset	Moderate inconsistency (I ² = 43.0%)	16/325 (4.9%) [3.2, 7.7]	15/313 (4.8%) [0.7, 10.0]	RR: 1.22 (0.39, 3.81)	Some limitations
6 (13-16, 18, 19)	Headache	Moderate inconsistency (I ² = 43.0%)	83/800 (10.4%) [2.6, 14.6]	55/805 (6.8%) [3.2, 16.2]	RR: 1.50 (0.94, 2.38)	Some limitations
2 (13, 14)	Hostility	No important inconsistency (I ² = 0.0%)	18/286 (6.3%) [2.8, 9.7]	19/290 (6.6%) [5.6, 7.5]	RR: 0.91 (0.37, 2.21)	Some limitations
6 (9, 10, 12, 13, 15, 18)	Insomnia	No important inconsistency (I ² = 0.0%)	89/899 (9.9%) [5.2, 25.0]	38/859 (4.4%) [0.0, 14.3]	RR: 2.19 (1.51, 3.17)	Some limitations
3 (12, 17, 18)	Muscle cramps and leg cramps	High inconsistency (I ² = 52.5%)	26/331 (7.9%) [7.6, 12.5]	9/329 (2.7%) [0.6, 14.3]	RR: 2.46 (0.67, 9.04)	Some limitations
2 (18, 19)	Nasal congestion	No important inconsistency (I ² = 0.0%)	7/197 (3.6%) [3.2, 5.1]	9/193 (4.7%) [3.9, 7.5]	RR: 0.77 (0.29, 2.02)	Some limitations
11 (9, 10, 12-18, 20, 33)	Nausea	No important inconsistency (I ² = 0.0%)	204/1451 (14.1%) [6.3, 25.0]	76/1412 (5.4%) [0.0, 9.0]	RR: 2.54 (1.97, 3.29)	Some limitations
3 (16, 18, 19)	Pain	No important inconsistency (I ² = 23.2%)	44/300 (14.7%) [5.1, 20.4]	35/298 (11.7%) [2.5, 21.9]	RR: 1.27 (0.75, 2.13)	Some limitations
2 (14, 18)	Respiratory tract infection	No important inconsistency (I ² = 0.0%)	21/302 (7.0%) [3.2, 11.1]	22/299 (7.4%) [3.9, 11.0]	RR: 0.96 (0.54, 1.70)	Some limitations
3 (15, 16, 17)	Rhinitis	No important inconsistency (I ² = 0.0%)	51/474 (10.8%) [5.7, 16.5]	34/484 (7.0%) [2.5, 15.2]	RR: 1.49 (0.99, 2.26)	Some limitations
7 (13-16, 18, 19, 33)	Urinary tract infection	High inconsistency (I ² = 58.9%)	90/928 (9.7%) [2.6, 17.2]	92/925 (9.9%) [4.1, 20.0]	RR: 0.93 (0.58, 1.50)	Some limitations

7 (9, 12, 14, 16-18, 20)	Vomiting	Moderate inconsistency (I ² = 50.4 %)	98/871 (11.3%) [5.0, 16.1]	41/874 (4.7%) [0.0, 14.3]	RR: 2.25 (1.26, 4.03)	Some limitations
4 (14, 15, 16, 18)	Weight Loss	No important inconsistency (I ² = 0.0%)	51/619 (8.2%) [5.1, 19.4]	28/621 (4.5%) [2.0, 9.5]	RR: 1.83 (1.18, 2.86)	Some limitations
Donepezil vs. placebo (Vascular dementia)						
21 (22, 23)	Abnormal dreams	No important inconsistency (I ² = 0.0%)	24/421 (5.7%) [5.1, 6.3]	5/392 (1.3%) [0.5, 2.0]	RR: 4.07 (1.54, 10.74)	Some limitations
2	Anorexia	High inconsistency (I ² = 68.5%)	36/421 (8.6%) [8.3, 8.8]	14/392 (3.6%) [1.5, 5.7]	RR: 2.65 (0.77, 9.15)	Some limitations
2	Diarrhea	No important inconsistency (I ² = 0.0%)	70/421 (16.6%) [14.6, 18.6]	40/392 (10.2%) [10.1, 10.4]	RR: 1.62 (1.13, 2.34)	Some limitations
2	Headache	Moderate inconsistency (I ² = 43.4%)	29/421 (6.9%) [6.5, 7.3]	25/392 (6.4%) [4.5, 8.3]	RR: 1.09 (0.54, 2.20)	Some limitations
2	Hypertension	No important inconsistency (I ² = 0.0%)	24/421 (5.7%) [5.3, 6.0]	20/392 (5.1%) [4.0, 6.2]	RR: 1.11 (0.62, 1.98)	Some limitations
2	Muscle cramps and leg cramps	No important inconsistency (I ² = 0.0%)	41/421 (9.7%) [6.0, 13.6]	4/392 (1.0%) [0.5, 1.5]	RR: 9.62 (3.48, 26.58)	Some limitations
2	Nausea	No important inconsistency (I ² = 0.0%)	69/421 (16.4%) [16.0, 16.7]	29/392 (7.4%) [7.0, 7.8]	RR: 2.21 (1.47, 3.34)	Some limitations
2	Rhinitis	Moderate inconsistency (I ² = 43.8%)	25/421 (5.9%) [5.1, 6.8]	7/392 (1.8%) [0.5, 3.0]	RR: 3.60 (0.90, 14.49)	Some limitations
2	Stroke	High inconsistency (I ² = 62.1%)	20/421 (4.8%) [3.7, 5.8]	17/392 (4.3%) [3.0, 5.7]	RR: 1.11 (0.38, 3.20)	Some limitations
2	Syncope	No important inconsistency (I ² = 0.0%)	19/421 (4.5%) [3.9, 5.1]	10/392 (2.6%) [1.5, 3.6]	RR: 1.72 (0.81, 3.67)	Some limitations
2	Vomiting	High inconsistency (I ² = 83.9%)	28/421 (6.7%) [5.1, 8.3]	22/392 (5.6%) [3.0, 8.3]	RR: 1.27 (0.29, 5.48)	Some limitations
Donepezil vs. placebo (mild cognitive impairment patients)						
2 (21, 32)	Abnormal dreams	No important inconsistency (I ² = 0.0%)	47/385 (12.2%) [6.7, 22.7]	9/396 (2.3%) [1.5, 3.6]	RR: 5.36 (2.67, 10.76)	No serious limitations
2	Diarrhea	No important	78/385 (20.3%)	27/396 (6.8%)	RR: 2.96	No serious

		inconsistency (I ² = 0.0%)	[16.6, 27.3]	[6.6, 7.3]	(1.95, 4.48)	limitations
2	Insomnia	High inconsistency (I ² = 56.3 %)	41/385 (10.6%) [10.6, 10.7]	12/396 (3.0%) [1.9, 5.1]	RR: 3.34 (1.27, 8.80)	No serious limitations
2	Muscle cramps and leg cramps	No important inconsistency (I ² = 0.0%)	53/385 (13.8%) [9.1, 16.2]	7/396 (1.8%) [1.5, 1.9]	RR: 7.73 (3.56, 16.8)	No serious limitations
2	Nausea	No important inconsistency (I ² = 1.7%)	41/385 (10.6%) [8.3, 15.2]	14/396 (3.5%) [1.9, 6.6]	RR: 2.92 (1.61, 5.31)	No serious limitations
2	Vomiting	High inconsistency (I ² = 56.4%)	27/385 (7.0%) [5.9, 9.1]	5/396 (1.3%) [0.0, 1.9]	RR: 6.22 (0.74, 52.19)	No serious limitations

Galantamine

Galantamine vs. placebo (Alzheimer's disease)

3 (40, 41, 45)	Abdominal Pain	High inconsistency (I ² = 77.1%)	52/624 (8.3%) [6.9, 10.9]	21/424 (5.0%) [1.6, 11.6]	RR: 1.76 (0.56, 5.55)	Some limitations
2 (45, 46)	Accidental injury	No important inconsistency (I ² = 0.0%)	24/478 (5.0%) [3.7, 7.9]	29/406 (7.1%) [5.6, 12.8]	RR: 0.64 (0.38, 1.08)	Some limitations
2 (45, 46)	Accidental Fall	No important inconsistency (I ² = 0.0%)	44/478 (9.2%) [6.1, 15.8]	33/406 (8.1%) [5.9, 16.3]	RR: 1.00 (0.65, 1.54)	Some limitations
4 (39, 40, 45, 46)	Agitation	Moderate inconsistency (I ² = 34.2%)	70/1012 (6.9%) [6.1, 8.1]	56/817 (6.9%) [0.8, 9.4]	RR: 1.02 (0.63, 1.65)	Some limitations
6 (39-42, 45, 46)	Anorexia	No important inconsistency (I ² = 0.0%)	154/1441 (10.7%) [6.7, 20.4]	34/1245 (2.7%) [0.0, 5.6]	RR: 3.41 (2.36, 4.93)	Some limitations
2 (39, 40)	Deaths	Moderate inconsistency (I ² = 34.0%)	3/534 (0.6%) [0.0, 1.1]	6/411 (1.5%) [1.4, 1.6]	RR: 0.42 (0.06, 2.81)	Some limitations
2 (45, 46)	Depression	No important inconsistency (I ² = 0.0%)	29/478 (6.1%) [4.9, 8.6]	13/406 (3.2%) [2.5, 5.8]	RR: 1.74 (0.92, 3.31)	Some limitations
6 (39, 41, 42, 44-46)	Diarrhea	Moderate inconsistency (I ² = 29.0%)	128/1234 (10.4%) [3.7, 19.4]	90/1207 (7.5%) [2.3, 14.0]	RR: 1.30 (0.94, 1.79)	Some limitations
6 (40-42, 44- 46)	Dizziness	No important inconsistency (I ² = 0.0%)	158/1222 (12.9%) [7.4, 18.5]	66/1046 (6.3%) [3.4, 11.6]	RR: 1.90 (1.43, 2.51)	Some limitations
4 (40-42, 44- 46)	Headache	High inconsistency	60/750 (8.0%) [5.5, 14.8]	39/708 (5.5%) [3.3, 11.6]	RR: 1.49 (0.61, 3.63)	Some limitations

		(I ² = 77.8%)				
7 (39-42, 44-46)	Nausea	High inconsistency (I ² = 83.7%)	407/1495 (27.2%) [13.8, 43.6]	124/1332 (9.3%) [3.4, 27.9]	RR: 2.84 (1.76, 4.61)	Some limitations
2 (45, 46)	Respiratory tract infection	No important inconsistency (I ² = 0.0%)	24/478 (5.0%) [3.7, 7.9]	21/406 (5.2%) [5.0, 5.8]	RR: 0.91 (0.50, 1.65)	Some limitations
2 (45, 46)	Urinary tract infection	No important inconsistency (I ² = 0.0%)	34/478 (7.1%) [6.7, 7.9]	31/406 (7.6%) [5.8, 8.1]	RR: 0.93 (0.57, 1.50)	Some limitations
7 (39-42, 44-46)	Vomiting	Moderate inconsistency (I ² = 49.3%)	209/1495 (14.0%) [8.6, 25.6]	54/1332 (4.1%) [1.4, 10.5]	RR: 3.27 (2.13, 5.01)	Some limitations
3 (41, 42, 46)	Weight loss	No important inconsistency (I ² = 18.8%)	51/755 (6.8%) [5.0, 10.9]	15/748 (2.0%) [0.5, 8.1]	RR: 3.29 (1.66, 6.53)	Some limitations

Rivastigmine

Rivastigmine vs. placebo (Alzheimer's disease)

2 (53, 56)	Abdominal pain	No important inconsistency (I ² = 17.6%)	30/267 (11.2%) [4.2, 11.9]	8/259 (3.1%) [2.9, 5.0]	RR: 3.19 (1.03, 9.83)	Some limitations
4 (11, 51, 53, 56)	Anorexia	Moderate inconsistency (I ² = 38.9%)	90/543 (16.6%) [8.3, 19.9]	13/518 (2.5%) [0.0, 10.0]	RR: 5.34 (2.30, 12.42)	Some limitations
2 (50, 56)	Diarrhea	High inconsistency (I ² = 72.3%)	56/376 (14.9%) [12.0, 16.5]	23/372 (6.2%) [1.5, 8.8]	RR: 3.30 (0.80, 13.67)	Some limitations
5 (11, 51, 53, 56)	Dizziness	Moderate inconsistency (I ² = 39.1%)	143/676 (21.2%) [8.3, 26.7]	60/651 (9.2%) [0.0, 15.0]	RR: 2.24 (1.45, 3.46)	Some limitations
2 (51, 56)	Fatigue	No important inconsistency (I ² = 0.0%)	46/474 (9.7%) [9.5, 10.0]	15/474 (3.2%) [2.5, 3.8]	RR: 3.04 (1.72, 5.38)	Some limitations
4 (11, 50, 53, 56)	Headache	No important inconsistency (I ² = 0.0%)	71/445 (16.0%) [8.3, 18.5]	27/416 (6.5%) [0.0, 7.5]	RR: 2.43 (1.60, 3.70)	Some limitations
2 (51, 56)	Malaise	No important inconsistency (I ² = 0.0%)	30/474 (6.3%) [3.0, 9.5]	7/474 (1.5%) [0.9, 2.1]	RR: 4.24 (1.88, 9.55)	Some limitations
5 (11, 51, 53, 56)	Nausea	High inconsistency (I ² = 91.2%)	303/676 (44.8%) [16.7, 57.8]	74/651 (11.4%) [6.0, 58.3]	RR: 2.79 (1.26, 6.19)	Some limitations
5 (11, 51, 53, 56)	Vomiting	No important inconsistency (I ² = 14.1%)	188/676 (27.8%) [12.5, 37.8]	28/651 (4.3%) [3.0, 10.0]	RR: 6.06 (3.88, 9.45)	Some limitations

Memantine

Memantine vs. placebo (Alzheimer's disease)

3 (66, 69, 70)	Accidental fall	No important inconsistency ($I^2 = 0.0\%$)	48/699 (6.9%) [6.1, 7.5]	50/687 (7.3%) [7.0, 7.4]	RR: 0.95 (0.65, 1.39)	Some limitations
2 (69, 70)	Accidental injury	No important inconsistency ($I^2 = 3.1\%$)	22/404 (5.4%) [4.9, 6.0]	27/403 (6.7%) [5.4, 8.0]	RR: 0.82 (0.47, 1.43)	Some limitations
4 (66, 68, 69, 70)	Agitation	High inconsistency ($I^2 = 73.9\%$)	85/825 (10.3%) [3.7, 31.7]	82/813 (10.1%) [5.9, 18.3]	RR: 0.97 (0.54, 1.74)	Some limitations
3 (66, 69, 70)	Confusion	High inconsistency ($I^2 = 59.1\%$)	48/699 (6.9%) [5.0, 7.9]	32/687 (4.7%) [2.0, 7.4]	RR: 1.62 (0.75, 3.49)	Some limitations
3 (66, 68, 70)	Diarrhea	No important inconsistency ($I^2 = 0.0\%$)	31/624 (5.0%) [4.1, 7.9]	39/611 (6.4%) [3.5, 9.5]	RR: 0.79 (0.50, 1.25)	Some limitations
3 (66, 69, 70)	Dizziness	No important inconsistency ($I^2 = 0.0\%$)	57/699 (8.2%) [5.0, 11.2]	48/687 (7.0%) [4.5, 8.1]	RR: 1.16 (0.80, 1.68)	Some limitations
2 (69, 70)	Flu-like symptoms	No important inconsistency ($I^2 = 0.0\%$)	29/404 (7.2%) [7.0, 7.4]	26/403 (6.5%) [6.4, 6.5]	RR: 1.11 (0.67, 1.86)	Some limitations
3 (66, 69, 70)	Headache	No important inconsistency ($I^2 = 9.1\%$)	47/699 (6.7%) [6.4, 7.1]	33/687 (4.8%) [2.5, 6.7]	RR: 1.39 (0.87, 2.21)	Some limitations
2 (66, 68)	Insomnia	No important inconsistency ($I^2 = 19.5\%$)	18/421 (4.3%) [2.7, 7.9]	32/410 (7.8%) [6.7, 10.3]	RR: 0.56 (0.30, 1.06)	Some limitations
2 (69, 70)	Respiratory tract infection	Moderate inconsistency ($I^2 = 27.8\%$)	14/404 (3.5%) [2.0, 4.9]	25/403 (6.2%) [5.9, 6.5]	RR: 0.56 (0.25, 1.22)	Some limitations
3 (66, 68, 70)	Urinary incontinence	No important inconsistency ($I^2 = 0.0\%$)	36/624 (5.8%) [3.7, 11.1]	29/611 (4.7%) [3.0, 11.1]	RR: 1.21 (0.75, 1.95)	Some limitations
2 (68, 70)	Urinary tract infection	Moderate inconsistency ($I^2 = 29.8\%$)	29/329 (8.8%) [5.9, 13.5]	17/327 (5.2%) [5.0, 5.6]	RR: 1.68 (0.84, 3.39)	Some limitations

*Results of the meta-analyses were computed using a random effects model. RR = relative risk.