Appendix 3 (as supplied by the authors): GRADE evidence

Table 3. GRADE Evidence Profile: Effect of treatment for Mild Cognitive Impairment on Cognition

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Control	Mean Difference(95% CI)		
Effect of AChEIs on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention ranged from 11 to 48 months; follow-up: immediate post)											
4	randomised trials[1]	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	serious[5]	none[6]	2078	2110	-0.3343 (-0.7263 to 0.0577)	⊕⊕OO LOW	CRITICAL
Effect of Donepezil on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention ranged from 11 to 36 months; follow-up: immediate post)											
2	randomised trials[7]	serious[8]	no serious inconsistency[9]	no serious indirectness[10]	serious[1]	none[6]	632	637	-0.5966 (-1.3473 to 0.1542)	⊕⊕OO LOW	CRITICAL
Effect of Rivastigmine on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 48 months; follow-up: immediate post)											
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[16]	none[6]	508	510	0 (-0.7987 to 0.7987)	⊕⊕OO LOW	CRITICAL
Effect of Galantamine on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 24 months; follow-up: immediate post)											
1	randomised trials[17]	serious[18]	no serious inconsistency[14]	no serious indirectness[19]	serious[20]	none[6]	938	963	-0.2073 (-0.7951 to 0.3805)	⊕⊕OO LOW	CRITICAL
Effect of AChEIs on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 11 to 48 months; follow-up: immediate post)											
3	randomised trials[21]	serious[22]	no serious inconsistency[23]	no serious indirectness[24]	serious[25]	none[6]	1140	1147	0.1682 (-0.1330 to 0.4694)	⊕⊕OO LOW	CRITICAL
Effect of Donepezil on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 11 to 36 months; follow-up: immediate post)											
2	randomised trials[7]	serious[8]	no serious inconsistency[26]	no serious indirectness[10]	serious[27]	none[6]	632	637	0.2376 (-0.1902 to 0.6653)	⊕⊕OO LOW	CRITICAL
Effect of Rivastigmine on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention: 48 months; follow-up: immediate post)											
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[28]	none[6]	508	510	0.1000 (-0.3242 to 0.5242)	⊕⊕OO LOW	CRITICAL
Effect of Dietary supplements on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 36 months; follow-up: immediate post)											
1	randomised trials[29]	serious[30]	no serious inconsistency[14]	no serious indirectness[31]	serious[32]	none[6]	257	259	0.8500 (-0.3161 to 2.0161)	⊕⊕OO LOW	CRITICAL
Effect of Dietary supplements on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 12 to 36 months; follow-up: immediate post)											

Appendix to: Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. *CMAJ Open* 2015. DOI:10.9778/cmajo.20150057.

4	randomised trials[33]	serious[34]	no serious inconsistency[35]	no serious indirectness[36]	serious[37]	none[6]	511	519	0.1959 (-0.0403 to 0.4321)	⊕⊕OO LOW	CRITICAL
Effect of non-pharma interventions on Cognition (measured with: ADAS-Cog; Better indicated by lower values) (length of intervention: 6 months; follow-up: immediate post)											
1	randomised trials[38]	no serious risk of bias[39]	no serious inconsistency[14]	no serious indirectness[40]	serious[41]	none[6]	47	45	-0.6000 (-1.4421 to 0.2421)	⊕⊕⊕O MODERATE	CRITICAL
Effect of non-pharma interventions on Cognition (measured with: MMSE; Better indicated by higher values) (length of intervention ranged from 6 to 12 months; follow-up: immediate post)											
5	randomised trials[42]	serious[43]	no serious inconsistency[44]	no serious indirectness[45]	no serious imprecision[46]	none[6]	221	187	1.0072 (0.2475 to 1.7668)	⊕⊕⊕O MODERATE	CRITICAL

Table 4. Summary of Findings: Treatment for Mild Cognitive Impairment (Cognition)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Risk difference with Treatment (95% CI)
Effect of AChEIs on Cognition ADAS-Cog	4188 (4 studies[1])	⊕⊕⊖⊖ **LOW**[2,3,4,5,6] due to risk of bias, imprecision	The mean effect of AChEIs on cognition in the intervention groups was **0.3343 lower** (0.7263 lower to 0.0577 higher)
Effect of Donepezil on Cognition ADAS-Cog	1269 (2 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,9,10,11] due to risk of bias, imprecision	The mean effect of Donepezil on cognition in the intervention groups was **0.5966 lower** (1.3473 lower to 0.1542 higher)
Effect of Rivastigmine on Cognition ADAS-Cog	1018 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,16] due to risk of bias, imprecision	The mean effect of Rivastigmine on cognition in the intervention groups was **0 higher** (0.7987 lower to 0.7987 higher)
Effect of Galantamine on Cognition ADAS-Cog	1901 (1 study[17])	⊕⊕⊖⊖ **LOW**[6,14,18,19,20] due to risk of bias, imprecision	The mean effect of Galantamine on cognition in the intervention groups was **0.2073 lower** (0.7951 lower to 0.3805 higher)
Effect of AChEIs on Cognition MMSE	2287 (3 studies[21])	⊕⊕⊖⊖ **LOW**[6,22,23,24,25] due to risk of bias, imprecision	The mean effect of AChEIs on cognition in the intervention groups was **0.1682 higher** (0.1330 lower to 0.4694 higher)
Effect of Donepezil on Cognition MMSE	1269 (2 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,10,26,27] due to risk of bias, imprecision	The mean effect of Donepezil on cognition in the intervention groups was **0.2376 higher** (0.1902 lower to 0.6653 higher)
Effect of Rivastigmine on Cognition MMSE	1018 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,28] due to risk of bias, imprecision	The mean effect of Rivastigmine on cognition in the intervention groups was **0.1000 higher** (0.3242 lower to 0.5242 higher)
Effect of Dietary supplements on	516 (1 study[29])	⊕⊕⊖⊖	The mean effect of Dietary supplements on cognition in the intervention groups was **0.8500 higher**

Cognition ADAS-Cog		**LOW**[6,14,30,31,32] due to risk of bias, imprecision	(0.3161 lower to 2.0161 higher)
Effect of Dietary supplements on Cognition MMSE	1030 (4 studies[33])	⊕⊕⊖⊖ **LOW**[6,34,35,36,37] due to risk of bias, imprecision	The mean effect of Dietary supplements on cognition in the intervention groups was **0.1959 higher** (0.0403 lower to 0.4321 higher)
Effect of non-pharma interventions on Cognition ADAS-Cog	92 (1 study[38])	⊕⊕⊕⊖ **MODERATE**[6,14,39,40,41] due to imprecision	The mean effect of non-pharma interventions on cognition in the intervention groups was **0.6000 lower** (1.4421 lower to 0.2421 higher)
Effect of non-pharma interventions on Cognition MMSE	408 (5 studies[42])	⊕⊕⊕⊖ **MODERATE**[6,43,44,45,46] due to risk of bias	The mean effect of non-pharma interventions on cognition in the intervention groups was **1.0072 higher** (0.2475 to 1.7668 higher)

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Feldman et. al, 2007; 4) Winblad et. al, 2008.

[2] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 3 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (50%); and high risk of bias associated with incomplete outcome reporting (25%) and other sources of bias (75%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] The statistical heterogeneity is minimal [Chi2=4.63, df=4 (P=0.33); I2=14%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[4] Four RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 69 to 74 years. The intervention arm received Donepezil (10 mg/day) in two studies, Rivastigmine (3-12 mg/day) in one study and Galantamine (16-24 mg/day) in one study. The control group across all studies received placebo. Two studies were conducted in US and Canada, one in US and one in 14 countries. All studies were published from 2005 to 2009. The length of intervention across four studies ranged from 11 to 48 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[5] The sample size is adequate i.e. > 300 (2078 intervention arm, 2110 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= -0.3343 (-0.7263, 0.0577)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[6] There were too few studies (n<10) to assess publication bias.

[7] 1) Doody et. al, 2009; 2) Petersen et. al 2005.

[8] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and one as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (50%); and high risk associated with other sources of bias (50%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] The statistical heterogeneity is minimal [Chi2=1.48, df=1 (P=0.22); I2=33%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[10] Two RCTs provided data for this outcome. Both studies included mixed gender samples. The mean age across studies ranged from 70 to 74 years. The intervention arm received Donepezil (10 mg/day) and the control group received placebo. One study was conducted in US and one in US and Canada. One study was published in 2005 and one in 2009. The length of intervention across studies

ranged from 11 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[11] The sample size is adequate i.e. > 300 (632 intervention arm, 637 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= -0.5966 (-1.3473, 0.1542)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] Feldman et. al, 2007

[13] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[14] The statistical heterogeneity across studies could not be assessed due to only one study providing data for this outcome.

[15] One RCT provided data for this outcome. The study included a mixed gender sample. The mean age was 70.6 years for the intervention group and 70.3 years for the control group. The intervention arm received Rivastigmine (3-12 mg/day). The control group received placebo. The study was conducted in 14 countries and published in 2007. The length of intervention was 48 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[16] The sample size is adequate i.e. > 300 (508 intervention arm, 510 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.0 (-0.7987, 0.7987)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[17] Winblad et. al, 2008.

[18] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment; and high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[19] One RCT provided data for this outcome. The study included a mixed gender sample. The study included results from two trials with mean age as 69.2 years for the intervention group and 70.1 years for the control group in one trial and mean age of 70.6 years for the intervention group and 70.9 years for the control group in the 2nd trial. The intervention arm received galantamine (16-24 mg/day) in both trials. The control group received placebo. The study was conducted in the US and Canada and published in 2008. The length of intervention was 24 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[20] The sample size is adequate i.e. > 300 (938 intervention arm, 963 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= -0.2073 (-0.7951, 0.3805)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[21] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Feldman et. al, 2007

[22] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 2 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (33%), and allocation concealment (33%); and high risk of bias associated with incomplete outcome reporting (33%) and other sources of bias (67%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[23] The statistical heterogeneity is minimal [Chi^2=0.79, df=2 (P=0.68); I^2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[24] Three RCTs provided data for this outcome. All studies included mixed gender samples. The mean age across studies ranged from 69 to 74 years. The intervention arm received Donepezil (10 mg/day) in two studies and Rivastigmine (3-12 mg/day) in one study. The control group across all studies received placebo. One study was conducted in US and Canada, one in US and one in 14 countries. All studies were published from 2005 to 2009. The length of intervention across four studies ranged from 11 to 48 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[25] The sample size is adequate i.e. > 300 (1140 intervention arm, 1147 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= 0.1682 (-0.1330, 0.4694)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[26] The statistical heterogeneity is minimal [Chi^2=0.58, df=1 (P=0.44); I^2=0%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[27] The sample size is adequate i.e. > 300 (632 intervention arm, 637 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.2376 (-0.1902, 0.6653)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[28] The sample size is adequate i.e. > 300 (508 intervention arm, 510 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "0" [MD= 0.1 (-0.3242, 0.5242)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[29] Petersen et. al 2005.

[30] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment. Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[31] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 72.8 years for the intervention group and 72.9 years for the control group. The intervention arm received Donepezil (10 mg/day). The control group received placebo. The study was conducted in US and Canada, and published in 2005. The length of intervention was 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[32] The sample size is not adequate i.e. < 300 (257 intervention arm, 259 control arm) and the pooled effect estimate is not precise with a confidence interval that includes the null value "0" [MD= 0.8500 (-0.3161, 2.0161)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[33] 1) Petersen et. al, 2005; 2) de Jager et. al, 2012; 3) Lee et. al, 2013; 4) Naeini et. al, 2014.

[34] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 3 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (50%), and allocation concealment (75%); and high risk associated with other sources of bias (25%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[35] The statistical heterogeneity is minimal [Chi2=1.36, df=3 (P=0.71); I2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[36] Four RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 66 to 77 years. The intervention arm received Vitamin E in one study, Vitamin E and folic acid in one study, DHA (fish oil) in one study and Vitamins E and C in one study. The control group across all studies received placebo. One study was conducted in US and Canada, one in UK, one in Malaysia and one in Iran. All studies were published from 2005 to 2014. The length of intervention across four studies ranged from 12 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[37] The sample size is adequate i.e. > 300 (511 intervention arm, 519 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "0" [MD= 0.1959 (-0.0403, 0.4321)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[38] Suzuki et. al, 2013

[39] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as low risk. There were no serious concerns regarding risk of bias and this body of evidence was not downgraded for serious study limitations.

[40] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 74.8 years for the intervention group and 75.8 years for the control group. The intervention arm received a multi-component exercise program: biweekly. The control group received minimal contact with two education classes about health promotion. The study was conducted in Japan and published in 2013. The length of intervention was 6 months. There were no serious concerns regarding indirectness for this body of evidence and was not downgraded.

[41] The sample size is not adequate i.e. < 300 (47 intervention arm, 45 control arm) and the pooled effect estimate is not precise with confidence interval including the null value "0" [MD= -0.6000 (-1.4421, 0.2421)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[42] 1) Suzuki et. al, 2012; 2) Tsolaki. al, 2009; 3) Wei et. al, 2014; 4) Suzuki et. al, 2013: 5) Rojas et. al, 2013.

[43] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 4 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (80%), allocation concealment (80%), blinding (20%), incomplete outcome reporting (20%) and other sources of bias (20%); and high risk of bias associated with blinding (20%), incomplete outcome reporting (20%) and other sources of bias (40%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[44] The statistical heterogeneity is high [Chi^2=16.92, df=4 (P=0.002); I^2=76%] but the direction of the effect is consistent across studies and the confidence intervals overlap across most studies. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[45] Five RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 65 to 77 years. The intervention arm received multi-component exercise programs in three studies and cognitive training and rehabilitation in two studies. The control group across studies either received no therapy, waitlist or minimal contact involving education about health promotion. Two studies were conducted in Japan, one in China, one in Greece and one in Argentina. All studies were published from 2009 to 2014. The length of intervention across four studies ranged from 6 to 12 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[46] The sample size is not adequate i.e. < 300 (221 intervention arm, 187 control arm) but the pooled effect estimate is precise with a narrow confidence interval [MD= 1.0072 (0.2475, 1.7668)]. This body of evidence was not downgraded for serious concerns regarding imprecision.

Table 5. GRADE Evidence Profile: Serious Adverse Events associated with AChEIs for Mild Cognitive Impairment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Serious Adverse Events	Control	Relative (95% CI)	Absolute per 1000		
Serious AE's associated with AChEIs for MCI (assessed with: Number of Events) (length of intervention ranged from 6 to 48 months; follow-up: immediate post)												
5	randomised trials[1]	serious[2]	no serious inconsistency[3]	no serious indirectness[4]	serious[5]	none[6]	393/2308 (17.0277%)	401/2314 (17.3293%)	RR 0.9750 (0.8622 to 1.1027)	4 fewer (from 24 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with Donepezil for MCI (assessed with: Number of Events) (length of intervention ranged from 6 to 36 months; follow-up: immediate post)												
3	randomised trials[7]	serious[8]	no serious inconsistency[9]	no serious indirectness[10]	serious[11]	none[6]	60/777 (7.7220%)	52/783 (6.6411%)	RR 1.1506 (0.8081 to 1.6381)	10 more (from 13 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with Rivastigmine for MCI (assessed with: Number of Events) (length of intervention: 48 months; follow-up: immediate post)												
1	randomised trials[12]	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[16]	none[6]	141/505 (27.9208%)	155/509 (30.4519%)	RR 0.9169 (0.7567 to 1.1110)	25 fewer (from 74 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Serious AE's associated with Galantamine for MCI (assessed with: Number of Events) (length of intervention: 24 months; follow-up: immediate post)												
1	randomised trials[17]	serious[18]	no serious inconsistency[14]	no serious indirectness[19]	serious[20]	none[6]	192/1026 (18.7135%)	194/1022 (19.9824%)	RR 0.9858 (0.8237 to 1.1799)	3 fewer (from 33 fewer to 34 more)	⊕⊕OO LOW	CRITICAL

Table 6. Summary of Findings: Serious Adverse Events for MCI treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	**Risk difference with Serious Adverse Events** (95% CI)
Serious AE's associated with AChEIs for MCI	4622 (5 studies[1])	⊕⊕⊖⊖ **LOW**[2,3,4,5,6] due to risk of bias, imprecision	**RR 0.9750** (0.8622 to 1.1027)	**Study population**	
				173 per 1000	**4 fewer per 1000** (from 24 fewer to 18 more)
Serious AE's associated with Donepezil for MCI	1560 (3 studies[7])	⊕⊕⊖⊖ **LOW**[6,8,9,10,11] due to risk of bias, imprecision	**RR 1.1506** (0.8081 to 1.6381)	**Study population**	
				66 per 1000	**10 more per 1000** (from 13 fewer to 42 more)
Serious AE's associated with Rivastigmine for MCI	1014 (1 study[12])	⊕⊕⊖⊖ **LOW**[6,13,14,15,16] due to risk of bias, imprecision	**RR 0.9169** (0.7567 to 1.1110)	**Study population**	
				305 per 1000	**25 fewer per 1000** (from 74 fewer to 34 more)
Serious AE's associated with Galantamine for MCI	2048 (1 study[17])	⊕⊕⊖⊖ **LOW**[6,14,18,19,20] due to risk of bias, imprecision	**RR 0.9858** (0.8237 to 1.1799)	**Study population**	
				190 per 1000	**3 fewer per 1000** (from 33 fewer to 34 more)

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Salloway et. al, 2004; 4) Feldman et. al, 2007; 5) Winblad et. al, 2008.

[2] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and 4 studies were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (60%), and allocation concealment (60%); and high risk of bias associated with incomplete outcome reporting (40%) and other sources of bias (80%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] The statistical heterogeneity is minimal [Chi^2=1.64, df=4 (P=0.80); I^2=0%] and the confidence intervals overlap across most studies. This body of evidence was not downgraded for inconsistency.

[4] Five RCTs provided data for this outcome. All studies included mixed gender samples. The mean age across studies ranged from 69 to 74 years. The intervention arm received Donepezil (10 mg/day) in three studies, Rivastigmine (3-12 mg/day) in one study and Galantamine (16-24 mg/day) in one study. The control group across all studies received placebo. Two studies were conducted in US and Canada, two in US and one in 14 countries. All studies were published from 2004 to 2009. The length of intervention across four studies ranged from 6 to 48 months. There were no serious concerns regarding indirectness for this

body of evidence and it was not downgraded.

[5] The sample size is adequate i.e. > 300 (2308 intervention arm, 2314 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 0.9750 (0.8622, 1.1027)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[6] There were too few studies (n<10) to assess publication bias.

[7] 1) Doody et. al, 2009; 2) Petersen et. al, 2005; 3) Salloway et. al, 2004.

[8] Using Cochrane's Risk of Bias tool, for this outcome one study was rated as low and two studies as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding sequence generation (67%), and allocation concealment (67%); and high risk of bias associated with incomplete outcome reporting (33%), and other sources of bias (67%; i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm,). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] The statistical heterogeneity is minimal [Chi^2=0.39, df=2 (P=0.82); I^2=0%] and the confidence intervals overlap across studies. This body of evidence was not downgraded for inconsistency.

[10] Three RCTs provided data for this outcome. All studies included mixed gender population. The mean age across studies ranged from 70 to 74 years. The intervention arm received Donepezil (10 mg/day) and the control group received placebo. Two studies were conducted in US and one in US and Canada. One study was published in 2004, one in 2005 and one in 2009. The length of intervention across studies ranged from 6 to 36 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[11] The sample size is adequate i.e. > 300 (777 intervention arm, 783 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 1.1506 (0.8081, 1.6381)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] Feldman et. al, 2007

[13] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm). Given that most of the information is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[14] The statistical heterogeneity across studies could not be assessed due to only one study providing data for this outcome.

[15] One RCT provided data for this outcome. The study included mixed gender population. The mean age was 70.6 years for the intervention group and 70.3 years for the control group. The intervention arm received Rivastigmine (3-12 mg/day). The control group received placebo. The study was conducted in 14 countries and published in 2007. The length of intervention was 48 months. There were no serious concerns regarding indirectness for this body of evidence and it was not downgraded.

[16] The sample size is adequate i.e. > 300 (505 intervention arm, 509 control arm) but the pooled effect estimate is not precise and the confidence interval includes the null value "1" [RR= 0.9169 (0.7567, 1.1110)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[17] Winblad et. al, 2008.

[18] Using Cochrane's Risk of Bias tool, for this outcome the included study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding sequence generation, and allocation concealment; and high risk of bias associated with incomplete outcome reporting and other sources of bias (i.e., industry funding, baseline differences between groups, insufficiently powered and/or sample size <30 per arm,). Given that the information is from a study with moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[19] One RCT provided data for this outcome. The study included a mixed gender sample. The study included results from two trials with mean age as 69.2 years for the intervention group and 70.1 years for the control group in one trial and mean age as 70.6 years for the intervention group and 70.9 years for the control group in 2nd trial. The intervention arm received Galantamine (16-24 mg/day) in both trials. The control group received placebo. The study was conducted in the US and Canada and published in 2008. The length of intervention was 24 months. There were no serious concerns regarding indirectness for this body of evidence and uit was not downgraded.

[20] The sample size is adequate i.e. > 300 (1026 intervention arm, 1022 control arm) but the pooled effect estimate is not precise and the confidence inte rval includes the null value "1" [RR= 0.9858 (0.8237, 1.1799)]. This body of evidence was downgraded for serious concerns regarding imprecision.