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Contributions and Letters

Reply

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We have read the commentary by Tariot et al. [1] with interest and are delighted that our paper has provoked additional discussion.

With regard to the presentation of the multiple metagraphs, our method of labeling did not include the term 'favors'. In figure 5 for example, the labels along the x-axis are either 'control' or 'experimental', unlike the new figure provided by Tariot et al., where the word 'favors' precedes each term. This word was omitted from the graphs in order to avoid indicating that there was any favorable response towards a particular group. The graph instead indicates that the control group showed higher Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) values, and this was correctly interpreted in our discussion [2] as a nonsignificant trend to favor combination therapy. A revised graph now contains a clarification in the legend (fig. 4). The confidence interval plots and labels were set to be consistent throughout the paper for better appreciation of the results between the various assessments used.

The observation regarding the standard deviation value is valid and a correction has been made. The corrected p value however still does not reach statistical significance (<0.05) after this adjustment. Lastly, we closely inspected the remaining calculations and found similar deviations involving values obtained from the study by Tariot et al. [3], and these have also been corrected (fig. 1–4). While these corrections do not lead to a change in the paper's final conclusions or recommendations, it shows that in the patients in the mild-to-severe group of Alzheimer's disease (AD), combination therapy does not reveal any benefit in cognitive, behavioral or functional assessments. The authors regret this error and are thankful to Tariot et al. [1] for contributing to the accuracy of the study.

In our approach, we chose to include all levels of dementia severity in a single analysis as a first step. In addition to the explanation provided in the discussion section of the article [2] and the concern about heterogeneity that might result from the inclusion of all severity levels

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Muayqil and Camicioli: Reply

Mild to severe Ia										
Study or Subgroup	Expe Mean	riment SD	al Total		ntrol SD T	otal		Std. Mean Difference IV, Random, 95% Cl		Std. Mean Difference IV, Random, 95% Cl
Howard et al. 2012 DMvsD	0.8	2.6	73	0	2.6	73	25.5%	0.31 [-0.02, 0.63]		
Porsteinsson (MMSE)	16.5	5.38	210	16.4	5.08	198	37.5%	0.02 [-0.18, 0.21]		•
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	37.0%	0.36 [0.16, 0.55]		•
Total (95% CI)			481			467	100.0%	0.22 [-0.02, 0.45]		
Heterogeneity: Tau ² = 0.03;	: $Chi^2 = 6$	5.09. df		P = 0.05					+.	<u> </u>
Test for overall effect: Z = 1									-10	-5 0 5 10 Control Experimental
lild to severe Ib										
Study or Subgroup	Exp Mean	erimen		(Mean	Control		l Weigh	Std. Mean Difference t IV, Random, 95% (Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsD		2.6					and the second se			IV, Kandom, 55% CI
Porsteinsson (ADAS-cog)		12.83		10	11.94				-	
Tariot et al. 2004	0.9	9.43							-	
			-0.50							
Total (95% CI)			485		?		2 100.09	% 0.20 [-0.08, 0.47	1	
Heterogeneity: $Tau^2 = 0.05$ Test for overall effect: $Z = 1$			r = 2 (P)	' = 0.01); $ ^{*} = 7$	7%			-10	-5 0 5 3
rest for overall effect: $Z = 1$	1.59 (P =	0.16)								Control Experimental
fild to severe										
a										
885	Even	erimen	tal		ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean			Mean		Total	Weight			IV, Random, 95% CI
Howard et al. 2012 DMvsM	5.00 893 51.50	2.63	73		2.63	76	28.2%			
Porsteinsson (MMSE)		5.38	210		5.08	198	36.0%			
Tariot et al. 2004		9.43	198		9.66	196	35.7%		- T	
T										
Total (95% CI)			481	(0	000 -		100.0%	0.29 [-0.01, 0.60	- I -	
Heterogeneity: $Tau^2 = 0.06$; Test for overall effect: $Z = 1$			df = 2	(P = 0.0)	006); l ²	= 809	6		-10	-5 0 5 Control Experimental
b Study or Subgroup		riment			ontrol	Total	Weight	Std. Mean Difference IV, Random, 95% C		Std. Mean Difference
	Mean	ND.	Total	Mean	20					
	Mean 1.5		Total 73	Mean 0	2.63	76				IV, Random, 95% Cl
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog)	Mean 1.5 -28.5	2.63	Total 73 214	0	2.63 11.94		29.3%	0.57 [0.24, 0.90)	IV, Random, 95% CI
Howard et al. 2012 DMvsM	1.5	2.63	73	0		76	29.3% 35.6%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15)]	IV, Random, 95% CI
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004	1.5 -28.5	2.63 12.83	73 214 198	0 -28	11.94	76 213 196	29.3% 35.6% 35.2%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)]]	IV, Kandom, 95% CI
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI)	1.5 -28.5 0.9	2.63 12.83 9.43	73 214 198 485	0 -28 -2.5	11.94 9.66	76 213 196 485	29.3% 35.6%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)))	
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004	1.5 -28.5 0.9 Chi ² = 13	2.63 12.83 9.43 3.31, d	73 214 198 485	0 -28 -2.5	11.94 9.66	76 213 196 485	29.3% 35.6% 35.2%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)]]	-5 0 5 1
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1.	1.5 -28.5 0.9 Chi ² = 13	2.63 12.83 9.43 3.31, d	73 214 198 485	0 -28 -2.5	11.94 9.66	76 213 196 485	29.3% 35.6% 35.2%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)))	-5 0 5 1 Control Experimental
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1.	1.5 -28.5 0.9 Chi ² = 13	2.63 12.83 9.43 3.31, d	73 214 198 485	0 -28 -2.5	11.94 9.66	76 213 196 485	29.3% 35.6% 35.2%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)))	-5 0 5 1
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1.	1.5 -28.5 0.9 Chi ² = 13	2.63 12.83 9.43 3.31, d	73 214 198 485	0 -28 -2.5	11.94 9.66	76 213 196 485	29.3% 35.6% 35.2%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)))	-5 0 5 1
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1.	1.5 -28.5 0.9 Chi ² = 13 .58 (P = 0	2.63 12.83 9.43 3.31, d	73 214 198 485 f = 2 (F	0 -28 -2.5 P = 0.00	11.94 9.66	76 213 196 485	29.3% 35.6% 35.2% 100.0%	0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55)))	-5 0 5 1
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1.	1.5 -28.5 0.9 Chi ² = 13 .58 (P = 0	2.63 12.83 9.43 3.31, d 0.11)	73 214 198 485 f = 2 (F	0 -28 -2.5 P = 0.00	11.94 9.66 91); I ² =	76 213 196 485 85%	29.3% 35.6% 35.2% 100.0%	6 0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55 0.28 [-0.07, 0.62]]] -10	-5 0 5 1 Control Experimental
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Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1. Ioderate to severe Study or Subgroup	1.5 -28.5 0.9 Chi ² = 1: .58 (P = 0 Expe Mean 0.8	2.63 12.83 9.43 3.31, d 0.11) sp	73 214 198 485 f = 2 (F tal Total	0 -28 -2.5 P = 0.00 Co Mean	11.94 9.66 01); I ² = 0ntrol <u>SD 1</u> 2.6	76 213 196 485 85%	29.3% 35.6% 35.2% 100.0% Weight	 0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55 0.28 [-0.07, 0.62] Std. Mean Difference IV, Random, 95% CI]] -10	-5 0 5 1 Control Experimental Std. Mean Difference
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Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1. Ioderate to severe Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 3 oderate to severe Study or Subgroup Howard et al. 2012 DMvsM Tariot et al. 2012 DMvsM Tariot et al. 2004	1.5 -28.5 0.9 Chi ² = 1: .58 (P = 0 Expe <u>Mean</u> 0.8 0.9 ; Chi ² = 0 3.95 (P < Expe <u>Mean</u> 1.5	2.63 12.83 9.43 3.31, d 0.11) 2.6 9.43 0.006, dl 0.0000 riment SD 2.63	73 214 198 485 f = 2 (F Total 73 198 271 f = 1 (F 1) al Total 73 198	0 -28 -2.5 P = 0.00 Co Mean 0 -2.5 P = 0.80 Co Mean 0	11.94 9.66 9.1); $I^2 =$ 9.66 9.66 9.66 9); $I^2 = 0$ 9.67 9.68 9.66	76 213 196 485 85% 70 196 269 0%	29.3% 35.6% 35.2% 100.0% Weight 27.1% 72.9% 100.0% Weight 30.3% 69.7%	5 0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55 5 0.28 [-0.07, 0.62] 5 0.28 [-0.07, 0.62] 5 0.28 [-0.07, 0.62] 5 0.31 [-0.02, 0.63] 0.31 [-0.02, 0.63] 0.36 [0.16, 0.55] 0.34 [0.17, 0.51] 5 0.34 [0.17, 0.51] 5 0.57 [0.24, 0.90] 0.36 [0.16, 0.55]	-10	-5 0 5 1 Control Experimental
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1. Ioderate to severe Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 3 oderate to severe Study or Subgroup Howard et al. 2012 DMvsM Tariot et al. 2004 Total (95% CI)	1.5 -28.5 0.9 Chi ² = 1: .58 (P = 0 Expe Mean 0.8 0.9 ; Chi ² = 0 3.95 (P < Expe Mean 1.5 0.9	2.63 12.83 9.43 3.31, d 0.11) 2.6 9.43 0.006, df 0.0002 riment <u>SD</u> 2.63 9.43	73 214 198 485 f = 2 (F Total 73 198 271 f = 1 (F 1) al 73 198 271 73 198 271	0 -28 -2.5 P = 0.00 Mean 0 -2.5 P = 0.80 Co Mean 0 -2.5	11.94 9.66 91); $l^2 = 0$ 9.66 9.66 9); $l^2 = 0$ 9.66 9); $l^2 = 0$ 9.66 9.66	76 213 196 485 85% 73 196 269 0% ⁷ 6 196 272	29.3% 35.6% 35.2% 100.0% Weight 27.1% 72.9% 100.0% Weight 30.3%	Std. Mean Difference IV, Random, 95% CI 0.34 [0.17, 0.51] 0.35 [0.16, 0.55]	-10	-5 0 5 1 Control Experimental
Howard et al. 2012 DMvsM Porsteinsson (ADAS-cog) Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 1. Ioderate to severe Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 3 oderate to severe Study or Subgroup Howard et al. 2012 DMvsM Tariot et al. 2004	1.5 -28.5 0.9 Chi ² = 1: .58 (P = 0 Expe Mean 0.8 0.9 ; Chi ² = 0 3.95 (P < Expe Mean 1.5 0.9 Chi ² = 1.	2.63 12.83 9.43 3.31, d 0.11) 2.6 9.43 0.006, df 0.0000 riment <u>SD</u> 2.63 9.43 2.63 9.43	73 214 198 485 f = 2 (F Total 73 198 271 f = 1 (F 1) al 73 198 271 73 198 271 = 1 (P	0 -28 -2.5 P = 0.00 Mean 0 -2.5 P = 0.80 Co Mean 0 -2.5	11.94 9.66 91); $l^2 = 0$ 9.66 9.66 9); $l^2 = 0$ 9.66 9); $l^2 = 0$ 9.66 9.66	76 213 196 485 85% 73 196 269 0% ⁷ 6 196 272	29.3% 35.6% 35.2% 100.0% Weight 27.1% 72.9% 100.0% Weight 30.3% 69.7%	 0.57 [0.24, 0.90 -0.04 [-0.23, 0.15 0.36 [0.16, 0.55 0.28 [-0.07, 0.62] 5.0.28 [-0.07, 0.62] 5.0.28 [-0.07, 0.62] 0.31 [-0.02, 0.63] 0.36 [0.16, 0.55] 0.34 [0.17, 0.51] 5.54. Mean Difference IV, Random, 95% CI 0.57 [0.24, 0.90] 0.36 [0.16, 0.55] 	-10	-5 0 5 1 Control Experimental

(For legend see next page.)

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Aild to severe I	Envour		imonto		Con	trol		Mean Difference		Mean Difference
Study or Subgroup	Favours	s exper SI		tal Me			tal Weigh			IV, Fixed, 95% CI
Howard et al. 2012 DMvsD	0.5	5.	2	73	0	5.2	73 36.1			
Porsteinsson et al. 2008	51.8	15.8	9 2	14	52 1	5.7 2	13 11.5	% -0.20 [-3.20, 2.80]		
Tariot et al. 2004	-2	7.0	4 1	98 -	3.4 7	.16 1	97 52.4	% 1.40 [-0.00, 2.80]		
Total (95% CI)			4	85		4	83 100.0	% 0.89 [-0.12, 1.91]		•
Heterogeneity: $Chi^2 = 1.22$, d	f = 2 (P =	0.54)	$I^2 = 09$	6					-10	
Test for overall effect: $Z = 1.7$									-10	-'5 Ó Ś 1'0 Control Experimental
Mild to severe II										
	Expe	riment	al	C	ontro	1	5	td. Mean Difference	5	td. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	1	IV, Random, 95% CI
Howard et al. 2012 DMvsM	2	5.67	73	0	5.67	76	23.0%	0.35 [0.03, 0.67]		
Porsteinsson et al. 2008	51.8	15.89	214	52	15.7	213	39.1%	-0.01 [-0.20, 0.18]		
Tariot et al. 2004	-2	7.04	198	-3.4	7.16	197	37.9%	0.20 [-0.00, 0.39]		
Total (95% CI)			485			486	100.0%	0.15 [-0.05, 0.35]		
							200.010	0120 [0100] 0100]		18 19 19 19
Heterogeneity: $Tau^{\epsilon} = 0.02^{\circ}$	$Chi^2 = 4$	40 df	= 7 (P	= 0.11	$1 \cdot 1^2 =$	55%				
Heterogeneity: $Tau^2 = 0.02$; Test for overall effect: $Z = 1$.			= 2 (P	= 0.11); $ ^2 =$	55%			-10	-5 0 5 10
Heterogeneity: Tau" = 0.02; Test for overall effect: Z = 1.			= 2 (P	= 0.11); I ² =	55%			-10	-5 0 5 10 Control Experimental
Test for overall effect: Z = 1. Moderate to severe I	51 (P = 0 Expe	o.13) erimen	tal	c	ontro	1		Std. Mean Difference		Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup	51 (P = 0 Expe Mean).13) erimen SD	tal Total	C Mean	ontro SD	l Total	Weight	IV, Random, 95% CI		Control Experimental
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD	51 (P = 0 Expe Mean 0.5).13) erimen <u>SD</u> 5.2	tal Total 73	C Mean 0	Contro SD 5.2	I Total 73	Weight 27.1%	IV, Random, 95% CI 0.10 [-0.23, 0.42]		Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup	51 (P = 0 Expe Mean 0.5).13) erimen SD	tal Total	C Mean 0	ontro SD	I Total 73	Weight 27.1%	IV, Random, 95% CI		Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI)	51 (P = 0 Expe Mean 0.5 -2	erimen SD 5.2 7.04	tal Total 73 198 271	C Mean 0 -3.4	contro SD 5.2 7.16	I Total 73 197 270	Weight 27.1%	IV, Random, 95% CI 0.10 [-0.23, 0.42]		Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004	51 (P = 0 Expe Mean 0.5 -2	erimen SD 5.2 7.04	tal Total 73 198 271	C Mean 0 -3.4	contro SD 5.2 7.16	I Total 73 197 270	Weight 27.1% 72.9%	IV, Random, 95% Cl 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39]		Control Experimental Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI)	$51 (P = 0)$ Expendence Mean 0.5 -2 $Chi^{2} = 0$	erimen SD 5.2 7.04	tal Total 73 198 271	C Mean 0 -3.4	contro SD 5.2 7.16	I Total 73 197 270	Weight 27.1% 72.9%	IV, Random, 95% Cl 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39]		Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I <u>Study or Subgroup</u> Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1	$51 (P = 0)$ Expendence Mean 0.5 -2 $Chi^{2} = 0$	erimen SD 5.2 7.04	tal Total 73 198 271	C Mean 0 -3.4	contro SD 5.2 7.16	I Total 73 197 270	Weight 27.1% 72.9%	IV, Random, 95% Cl 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39]		Control Experimental Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z = 1. Moderate to severe I <u>Study or Subgroup</u> Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe	$51 (P = 0)$ Expendence Mean 0.5 -2 $Chi^{2} = 0$	erimen SD 5.2 7.04	tal Total 73 198 271	C Mean 0 -3.4	contro SD 5.2 7.16	I Total 73 197 270	Weight 27.1% 72.9%	IV, Random, 95% Cl 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39]		Control Experimental Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z = 1. Moderate to severe I <u>Study or Subgroup</u> Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1	51 (P = 0) Expe <u>Mean</u> 0.5 -2 Chi ² = 0 .97 (P = 0)	erimen <u>SD</u> 5.2 7.04	tal Total 73 198 271 f = 1 (P	C Mean 0 -3.4 2 = 0.6	0); I ² :	I Total 73 197 270 = 0%	Weight 27.1% 72.9%	IV, Random, 95% Cl 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34]	-10	Control Experimental Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z = 1. Moderate to severe I <u>Study or Subgroup</u> Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II	51 (P = 0) Expe <u>Mean</u> 0.5 -2 Chi ² = 0 .97 (P = 0)	erimen <u>SD</u> 5.2 7.04 0.27, d 0.05)	tal <u>Total</u> 73 198 271 f = 1 (P tal	C Mean 0 -3.4 2 = 0.6	Contro SD 5.2 7.16 0); I ² =	l Total 73 197 270 = 0%	Weight 27.1% 72.9%	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference	-10	Control Experimental Std. Mean Difference IV, Random, 95% CI -5 0 5 1 Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II Study or Subgroup	51 (P = (<u>Expe</u> <u>Mean</u> 0.5 -2 Chi ² = C .97 (P = <u>Expe</u> <u>Mean</u>).13) srimen <u>SD</u> 5.2 7.04).27, di 0.05) erimen SD	tal <u>Total</u> 73 198 271 f = 1 (F tal Total	C Mean 0 -3.4 2 = 0.6 (Mean	Contro SD 5.2 7.16 0); I ² = Contro SD	I Total 73 197 270 = 0%	Weight 27.1% 72.9% 100.0% Weight	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference IV, Random, 95% C	-10	Control Experimental Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II Study or Subgroup Howard et al. 2012 DMvsM	51 (P = (<u>Expe</u> <u>Mean</u> 0.5 -2 Chi ² = C .97 (P = <u>Expe</u> <u>Mean</u> 2	0.13) erimen <u>SD</u> 5.2 7.04 0.27, d 0.05) erimen <u>SD</u> 5.67	tal 73 198 271 f = 1 (P tal Total 73	C Mean 0 -3.4 2 = 0.6 C Mean 0	Contro SD 5.2 7.16 0); I ² = Contro SD 5.67	I Total 73 197 270 = 0% I Total 76	Weight 27.1% 72.9% 100.0% Weight 27.2%	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference IV, Random, 95% C 0.35 [0.03, 0.67	-10	Control Experimental Std. Mean Difference IV, Random, 95% CI -5 0 5 1 Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II Study or Subgroup	51 (P = (<u>Expe</u> <u>Mean</u> 0.5 -2 Chi ² = C .97 (P = <u>Expe</u> <u>Mean</u> 2).13) srimen <u>SD</u> 5.2 7.04).27, di 0.05) erimen SD	tal <u>Total</u> 73 198 271 f = 1 (F tal Total	C Mean 0 -3.4 2 = 0.6 C Mean 0	Contro SD 5.2 7.16 0); I ² = Contro SD	I Total 73 197 270 = 0% I Total 76	Weight 27.1% 72.9% 100.0% Weight 27.2%	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference IV, Random, 95% C	-10	Control Experimental Std. Mean Difference IV, Random, 95% CI -5 0 5 1 Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II Study or Subgroup Howard et al. 2012 DMvsM	51 (P = (<u>Expe</u> <u>Mean</u> 0.5 -2 Chi ² = C .97 (P = <u>Expe</u> <u>Mean</u> 2	0.13) erimen <u>SD</u> 5.2 7.04 0.27, d 0.05) erimen <u>SD</u> 5.67	tal 73 198 271 f = 1 (P tal Total 73	C Mean 0 -3.4 2 = 0.6 C Mean 0	Contro SD 5.2 7.16 0); I ² = Contro SD 5.67	Total 73 197 270 = 0%	Weight 27.1% 72.9% 100.0% Weight 27.2%	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference IV, Random, 95% C 0.35 [0.03, 0.67	- <u>10</u>	Control Experimental Std. Mean Difference IV, Random, 95% CI -5 0 5 1 Control Experimental Std. Mean Difference
Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 1 Moderate to severe II Study or Subgroup Howard et al. 2012 DMvsM Tariot et al. 2004	51 (P = 0 <u>Expe</u> <u>Mean</u> 0.5 -2 Chi ² = 0 .97 (P = <u>Exp</u> <u>Mean</u> 2 -2	erimen <u>SD</u> 5.2 7.04 0.27, di 0.05) erimen <u>SD</u> 5.67 7.04	tal 73 198 271 f = 1 (P tal Total 73 198 271	C Mean -3.4 P = 0.6 C Mean -3.4	Contro 5.2 7.16 0); l ² = 5.67 7.16	Total 73 197 270 = 0% Total 76 197 273	Weight 27.1% 72.9% 100.0% Weight 27.2% 72.8%	IV, Random, 95% CI 0.10 [-0.23, 0.42] 0.20 [-0.00, 0.39] 0.17 [0.00, 0.34] Std. Mean Difference IV, Random, 95% C 0.35 [0.03, 0.67 0.20 [-0.00, 0.39]	- <u>10</u>	Control Experimental Std. Mean Difference IV, Random, 95% CI -5 0 5 1 Control Experimental Std. Mean Difference

Fig. 2. Metagraphs of functional outcomes of mild-to-severe (3 studies) and moderate-to-severe (2 studies) subgroups. DMvsD = Combination therapy with donepezil and memantine versus monotherapy with donepezil, denoted by Roman numeral I; DMvsM = combination therapy with donepezil and memantine versus monotherapy with memantine, denoted by Roman numeral II. Scales used in each study: 23-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL₂₃) in Porsteinsson et al. [6], 19-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL₁₉) in Tariot et al. [3], and Bristol Activities of Daily Living Scale (BADLS) in Howard et al. [9]. Standardized mean differences were used to calculate effect sizes. A change in significance occurred in mild to severe I (p value changed from 0.01 to 0.08) and moderate to severe I (p value changed from 0.008 to 0.05).

Fig. 1. Metagraphs of cognitive outcomes of mild-to-severe (3 studies) and moderate-to-severe (2 studies) subgroups. DMvsD = Combination therapy with donepezil and memantine versus monotherapy with donepezil, denoted by Roman numeral I; DMvsM = combination therapy with donepezil and memantine versus monotherapy with memantine, denoted by Roman numeral II. In Porsteinsson et al. [6], Mini-Mental State Exam (MMSE) scores were pooled in the results, denoted as lower case 'a' and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) scores were pooled in the analysis, denoted as lower case 'b'. Howard et al. [9] used MMSE, and Tariot et al. [3] used Severe Impairment Battery (SIB). No change of significance occurred after correction.



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	Expe	rimenta		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Howard et al. 2012 DMvsD	5	11.09	73	0	11.09	73	29.6%	5.00 [1.40, 8.60]	
Porsteinsson et al. 2008	-12.9	14.48	212	-12.6	14.56	209	35.0%	-0.30 [-3.07, 2.47]	
Tariot et al. 2004	0.1	13.62	193	-3.7	13.6	189	35.3%	3.80 [1.07, 6.53]	
Total (95% CI)			478			471	100.0%	2.72 [-0.45, 5.89]	-
Heterogeneity: Tau ² = 5.45; C			2 (P =	= 0.04);	$l^2 = 709$	6		-	10 -5 0 5 10
Test for overall effect: $Z = 1.6$	58 (P = 0)	.09)							Control Experimental
Mild to severe II									
	Exp	eriment	al	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean			Weight	t IV, Random, 95% CI	
Howard et al. 2012 DMvsM	3.4	11.22	73		11.22		-		
Porsteinsson et al. 2008		14.48		-12.6				6 -0.30 [-3.07, 2.47]	
Tariot et al. 2004		13.62	193		13.6				
Total (95% CI)			478			474	100.0%	6 2.23 [-0.48, 4.94]	
Heterogeneity: $Tau^2 = 3.36$; Test for overall effect: $Z = 1$.					; I ² = 5		100.07	0 2.25 [-0.46, 4.54]	-10 -5 0 5 10 Control Experimental
Heterogeneity: $Tau^2 = 3.36$; Test for overall effect: $Z = 1$.					; I ² = 5		100.07	· 2.23 [-0.46, 4.34]	-10 -5 0 5 10
Heterogeneity: $Tau^2 = 3.36$; Test for overall effect: $Z = 1$.	61 (P =		= 2 (P	= 0.09)	ontrol	9%		Mean Difference	-10 -5 0 5 10
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe Study or Subgroup	61 (P = Expe Mean	0.11) eriment: SD	= 2 (P	= 0.09) C Mean	ontrol SD	9%			-10 -5 0 5 10 Control Experimental
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe	61 (P = Expe Mean	0.11) erimenta	= 2 (P	= 0.09) C Mean	ontrol	9%		Mean Difference	-10 -5 0 5 10 Control Experimental
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe Study or Subgroup	61 (P = Expe Mean	0.11) eriment: SD	al Total	= 0.09) C Mean	ontrol SD 11.09	9% Total	Weight	Mean Difference IV, Random, 95% CI	-10 -5 0 5 10 Control Experimental
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004	61 (P = Expe Mean 5	0.11) erimenta SD 11.09	al Total 73 193	= 0.09) C <u>Mean</u> 0	ontrol SD 11.09	9% Total 73 189	Weight 36.5% 63.5%	Mean Difference IV, Random, 95% CI 5.00 [1.40, 8.60] 3.80 [1.07, 6.53]	-10 -5 0 5 10 Control Experimental
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI)	Expe Mean 5 0.1	0.11) eriment: <u>SD</u> 11.09 13.6	al Total 73 193 266	= 0.09) C Mean 0 -3.7	ontrol SD 11.09 13.62	9% Total 73 189 262	Weight 36.5%	Mean Difference IV, Random, 95% CI 5.00 [1.40, 8.60] 3.80 [1.07, 6.53] 4.24 [2.06, 6.41]	Mean Difference IV, Random, 95% CI
Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00;	$61 (P = \frac{Expe}{Mean}$ $5 = 0.1$ $Chi^{2} = 0$	0.11) eriment: SD 11.09 13.6	al Total 73 193 266 = 1 (P	= 0.09) C Mean 0 -3.7	ontrol SD 11.09 13.62	9% Total 73 189 262	Weight 36.5% 63.5%	Mean Difference IV, Random, 95% CI 5.00 [1.40, 8.60] 3.80 [1.07, 6.53] 4.24 [2.06, 6.41]	Mean Difference IV, Random, 95% CI
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Heterogeneity: Tau ² = 3.36; Test for overall effect: Z = 1. Moderate to severe I Study or Subgroup Howard et al. 2012 DMvsD Tariot et al. 2004 Total (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 3.4 Moderate to severe II Study or Subgroup Howard et al. 2012 DMvsM	$61 (P = \frac{Expo}{Mean}$ 5 0.1 $Chi^2 = 0$ $82 (P = 0$ Exp Mean 3.4	0.11) eriment: <u>SD</u> 11.09 13.6 .27, df = 0.0001) eerimen <u>SD</u> 11.22	= 2 (P al Total 73 193 266 = 1 (P tal Total 73	= 0.09) Mean 0 -3.7 = 0.60); Mean 0 -3.7	$\frac{\text{ontrol}}{\text{SD}}$ 11.09 13.62 $I^{2} = 0\%$ Control SD 11.22	9% Total 73 189 262 6 Tota 76 189	Weight 36.5% 63.5% 100.0%	Mean Difference IV, Random, 95% CI 5.00 [1.40, 8.60] 3.80 [1.07, 6.53] 4.24 [2.06, 6.41] Mean Difference IV, Random, 95% C 3.40 [-0.20, 7.00 3.80 [1.07, 6.53]	Mean Difference IV, Random, 95% CI

Fig. 3. Metagraphs of behavioral outcomes of mild-to-severe (3 studies) and moderate-to-severe (2 studies) subgroups. DMvsD = Combination therapy with donepezil and memantine versus monotherapy with donepezil, denoted by Roman numeral I; DMvsM = combination therapy with donepezil and memantine versus monotherapy with memantine, denoted by Roman numeral II. Neuropsychiatric Inventory (NPI) scale was used in each study, and mean differences were used in determining effect sizes. A change in significance occurred in mild to severe I (p value changed from 0.03 to 0.08). No change of significance occurred in the moderate-to-severe subgroup analysis.

in the analysis, we add that our systematic review assessed many study types such as cohorts and open-label studies, some of which did use combination therapy in mild-to-moderate cases. As their results were not suitable for meta-analyses, it became necessary to analyze randomized controlled trials that included mild-to-severe cases. However, due to the broad clinical spectrum and the high I² scores obtained, it is more important to look at the subgroup analyses. A recent notable study also assessed mild-to-moderate AD patients that were already on cholinesterase inhibitor (ChEI). Patients were randomized to vitamin E, memantine or the two treatments in combination, and the results showed that only the vitamin E arm had slower functional decline compared with the placebo group (ChEI therapy) [4]. 128

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	Expe	erimen	tal	Control				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IN	V, Random	, 95% CI	
Porsteinsson 2008	4.38	1	214	4.42	0.96	213	52.5%	-0.04 [-0.23, 0.15]				
Fariot 2004	4.41	1.05	198	4.66	1.05	196	47.5%	-0.25 [-0.46, -0.04]				
Fotal (95% CI)			412			409	100.0%	-0.14 [-0.35, 0.07]				
Heterogeneity: Tau ² =	0.01; 0	$chi^2 = 1$	2.18. d	f = 1 (F	9 = 0.1	(4); $ ^2 =$	54%		-10	L 	1	10

Fig. 4. Metagraph of performance on CIBIC-Plus, available from 2 studies. No change of significance occurred after correction. The scores were lower in the control group with combination therapy, suggesting therapy favors the experimental group if p values reached significance.

The noteworthy meta-analysis by Atri et al. [5] mentioned in the commentary assessed patients with moderate-to-severe AD, and among the methodological differences was the inclusion of patients only on donepezil as a ChEI and the exclusion of those on <10 mg/day. Our study's goal was to assess for a class effect arising from ChEI or memantine and, if enough studies were available, to conduct subgroup analyses with each individual ChEI. Despite the differences, both studies find a statistically significant effect in cognition and functional outcome in the moderate-to-severe groups, favoring combination therapy. A separate study included data from Tariot et al. [3], Porsteinsson et al. [6], and a third unpublished trial MEM-MD-50 [7] in a meta-analysis of moderate-to-severe cases of AD. While the authors also found statistical significance in favor of a combination therapy on cognition, the study similarly came to the conclusion that more evidence was required [8].

While there were limitations in the study by Howard et al. [9] and a concern about the longer follow-up duration, the study provided a comparison of combination therapy with a memantine monotherapy arm. Thus, it helped in determining which treatment arm the benefits can be attributed to and was also in line with our a priori research objective. Even though the I² scores were low in the moderate-to-severe subgroup analyses, this does not exclude clinical or methodological heterogeneity. Including the study by Howard et al. in the meta-analysis was helpful, since patients are not treated for only 24 weeks in clinical practice. Given the broad spectrum from mild-to-severe stages of AD when donepezil can be used, it is likely that clinicians encounter patients who have been treated for much longer periods of time. Analyzing the two studies together provided us with a broader answer about the potential application of combination therapy; starting with a more generalized comparison followed by subgroup analyses to explore the causes of heterogeneity is an advantageous strategy [10] when conducting meta-analyses. Further subgroup analysis based on the duration of therapy was not done due to the small number of studies, which is a main reason for our conservative recommendation.

All these issues were taken into account when we drew our initial conclusions. Although there is no strong evidence against combining ChEI with memantine, we would like to take this opportunity to reiterate that original research exploring combination therapy is still required before confident recommendations can be made.

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