EXTRA Dementia and Geriatric Cognitive Disorders

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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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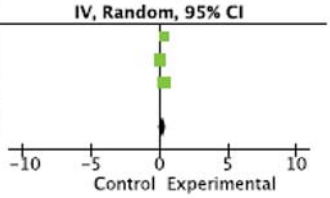
Mild to severe Ia

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
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]**

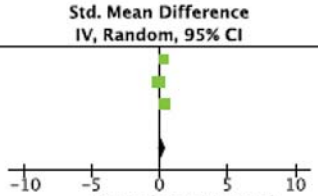
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.09$, df = 2 (P = 0.05); $I^2 = 67\%$
Test for overall effect: Z = 1.82 (P = 0.07)



Mild to severe Ib

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsD	0.8	2.6	73	0	2.6	73	27.4%	0.31 [-0.02, 0.63]
Porsteinsson (ADAS-cog)	-28.5	12.83	214	-28	11.94	213	36.6%	-0.04 [-0.23, 0.15]
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	36.0%	0.36 [0.16, 0.55]
Total (95% CI)			**485**			**482**	**100.0%**	**0.20 [-0.08, 0.47]**

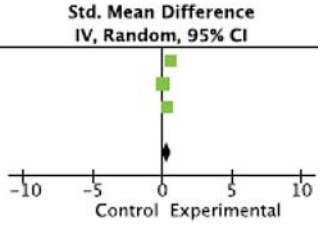
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.72$, df = 2 (P = 0.01); $I^2 = 77\%$
Test for overall effect: Z = 1.39 (P = 0.16)



Mild to severe IIa

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsM	1.5	2.63	73	0	2.63	76	28.2%	0.57 [0.24, 0.90]
Porsteinsson (MMSE)	16.5	5.38	210	16.4	5.08	198	36.0%	0.02 [-0.18, 0.21]
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	35.7%	0.36 [0.16, 0.55]
Total (95% CI)			**481**			**470**	**100.0%**	**0.29 [-0.01, 0.60]**

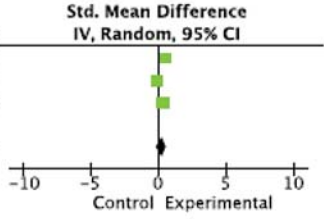
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 10.10$, df = 2 (P = 0.006); $I^2 = 80\%$
Test for overall effect: Z = 1.91 (P = 0.06)



Mild to severe IIb

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsM	1.5	2.63	73	0	2.63	76	29.3%	0.57 [0.24, 0.90]
Porsteinsson (ADAS-cog)	-28.5	12.83	214	-28	11.94	213	35.6%	-0.04 [-0.23, 0.15]
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	35.2%	0.36 [0.16, 0.55]
Total (95% CI)			**485**			**485**	**100.0%**	**0.28 [-0.07, 0.62]**

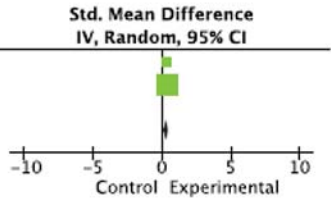
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 13.31$, df = 2 (P = 0.001); $I^2 = 85\%$
Test for overall effect: Z = 1.58 (P = 0.11)



Moderate to severe I

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsD	0.8	2.6	73	0	2.6	73	27.1%	0.31 [-0.02, 0.63]
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	72.9%	0.36 [0.16, 0.55]
Total (95% CI)			**271**			**269**	**100.0%**	**0.34 [0.17, 0.51]**

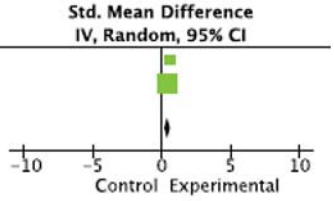
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = 3.95 (P < 0.0001)



Moderate to severe II

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Howard et al. 2012 DMvsM	1.5	2.63	73	0	2.63	76	30.3%	0.57 [0.24, 0.90]
Tariot et al. 2004	0.9	9.43	198	-2.5	9.66	196	69.7%	0.36 [0.16, 0.55]
Total (95% CI)			**271**			**272**	**100.0%**	**0.42 [0.23, 0.61]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, df = 1 (P = 0.28); $I^2 = 15\%$
Test for overall effect: Z = 4.31 (P < 0.0001)



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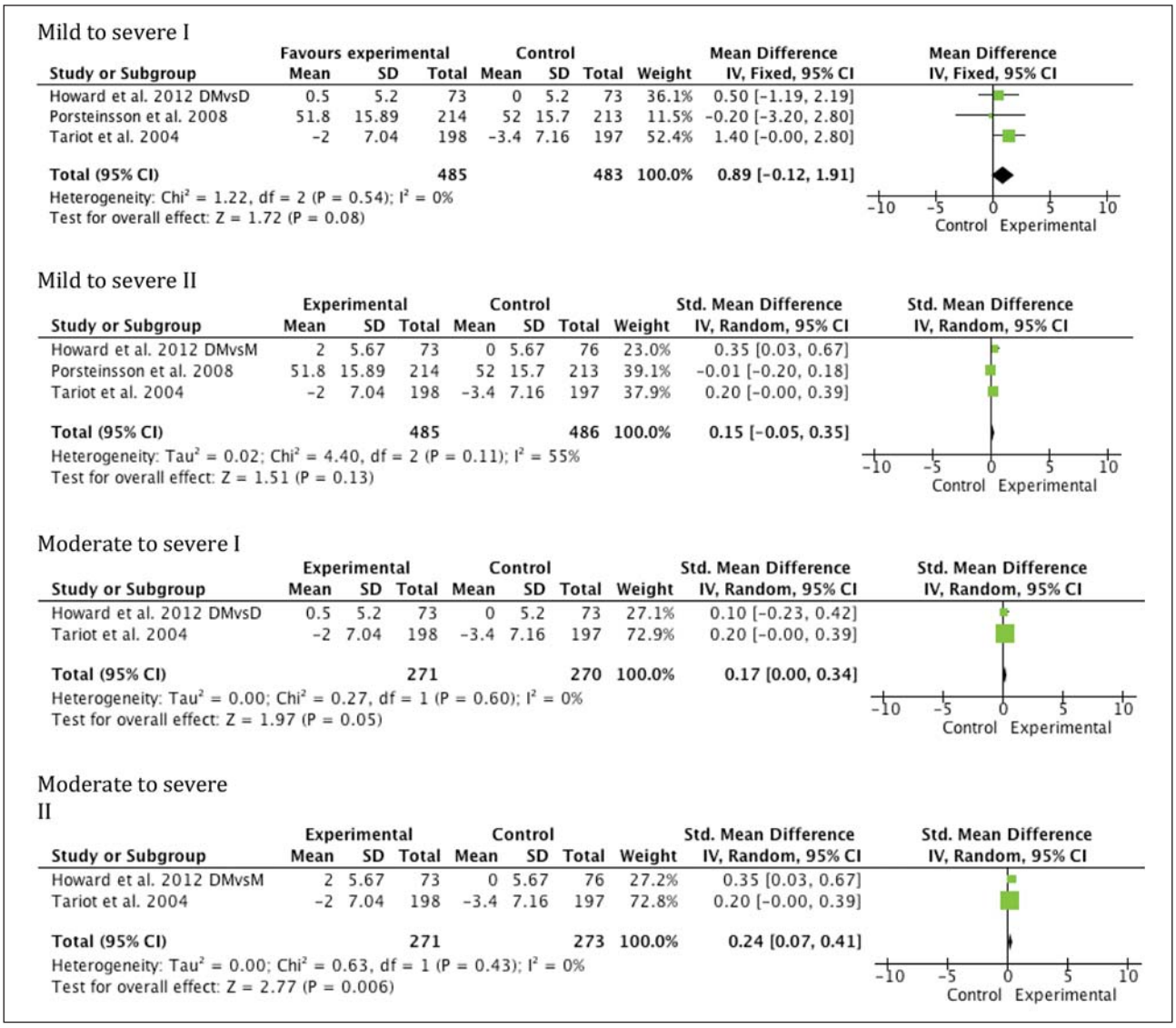

Fig. 2. Metagraphs of functional outcomes of mild-to-severe (3 studies) and moderate-to-severe (2 studies) subgroups. DMvsD = Combination therapy with donepezil and memantine versus monotherapy with donepezil, denoted by Roman numeral I; DMvsM = combination therapy with donepezil and memantine versus 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-ADL$_{23}$) in Porsteinsson et al. [6], 19-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL$_{19}$) 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.

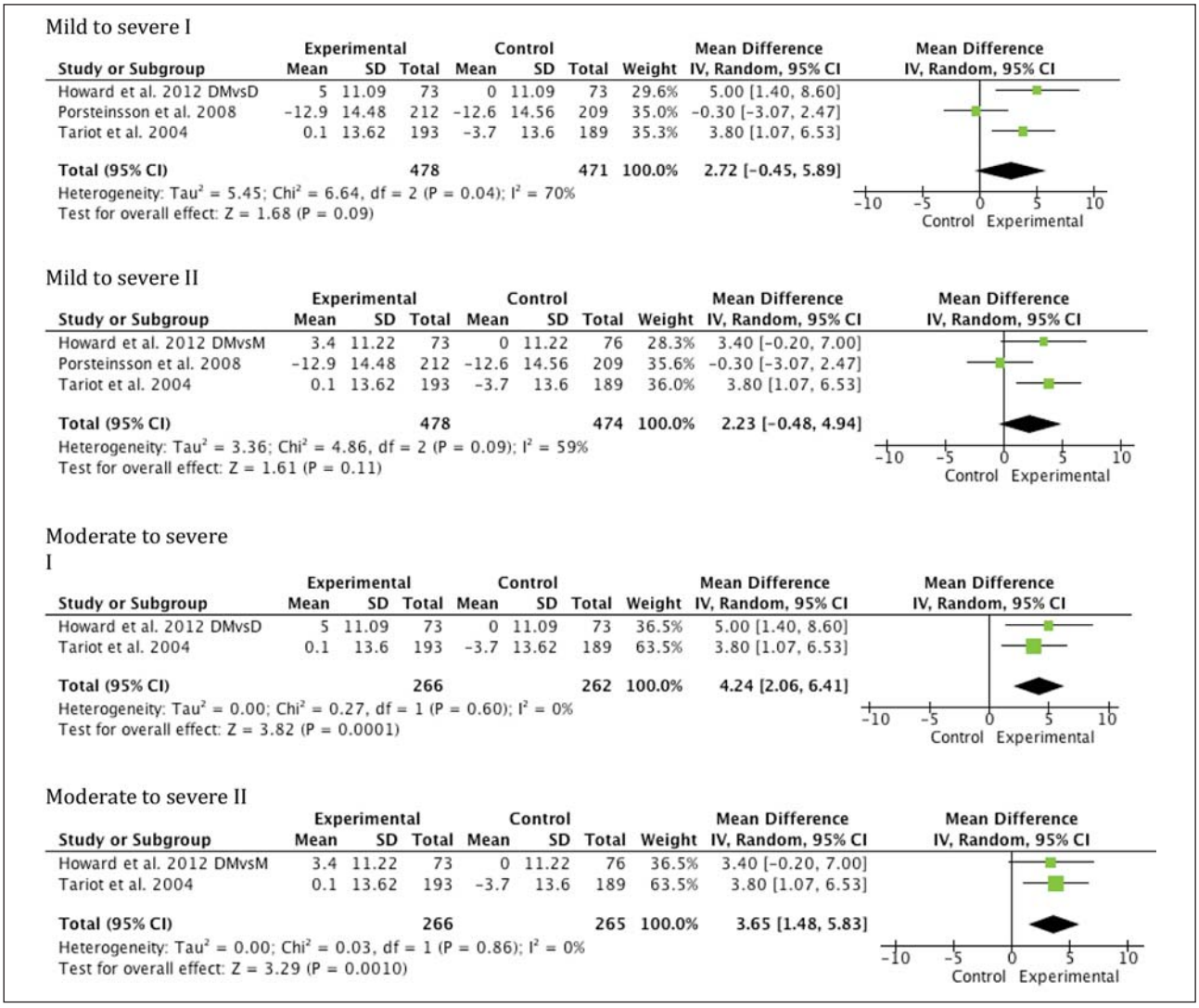

Fig. 3. Metagraphs of behavioral outcomes of mild-to-severe (3 studies) and moderate-to-severe (2 studies) subgroups. DMvsD = Combination therapy with donepezil and memantine versus monotherapy with donepezil, denoted by Roman numeral I; DMvsM = combination therapy with donepezil and memantine versus 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 I^2 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].

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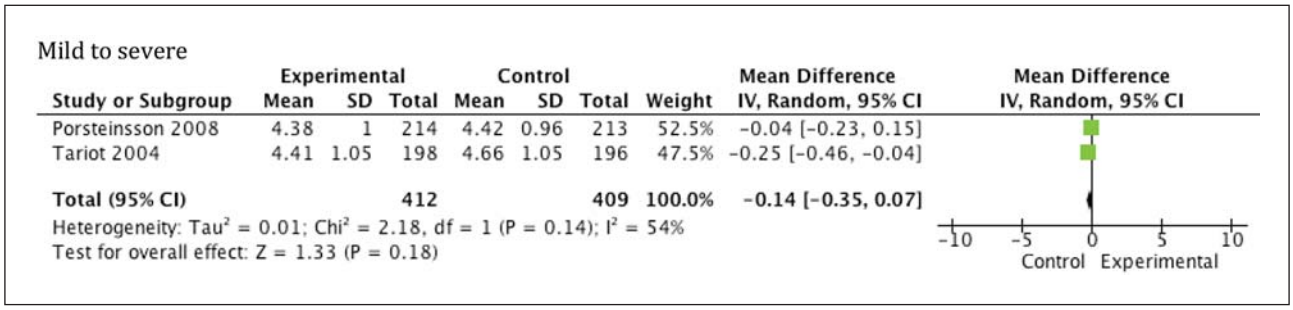

Fig. 4. Metagraph of performance on CIBIC-Plus, available from 2 studies. No change of significance occurred after correction. The scores were lower in the control group with combination therapy, suggesting therapy favors the experimental group if p values reached significance.

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 I^2 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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