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Contributions and Letters

Important Error in 'Systematic Review and Meta-Analysis of Combination Therapy with Cholinesterase Inhibitors and Memantine in Alzheimer's Disease and Other Dementias' by Muayqil and Camicioli

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After careful review of the article entitled 'Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer's disease and other dementias' [1], we have identified significant inaccuracies that we believe warrant attention and should be addressed.

A significant error is evident in figure 5. The numbers for the study that had been published by Tariot et al. [2], DPZ + MEM 4.41 and DPZ + PBO 4.66, are correct, but since the range of the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) scale goes from 1 to 7 with 7 being worst, the difference of –0.25 is in favor of experimental treatment and not as shown here in favor of the control. Additionally, the SD values for the MD-02 study are wrong. It seems that there may have been a mistake when calculating the SD from the SE values published in table 2 in the paper of Tariot et al. Both SDs are 1.05. This figure should be corrected to accurately portray the data reflecting the impact of combination therapy.

Figure 5 in Muayqil and Camicioli [1]:

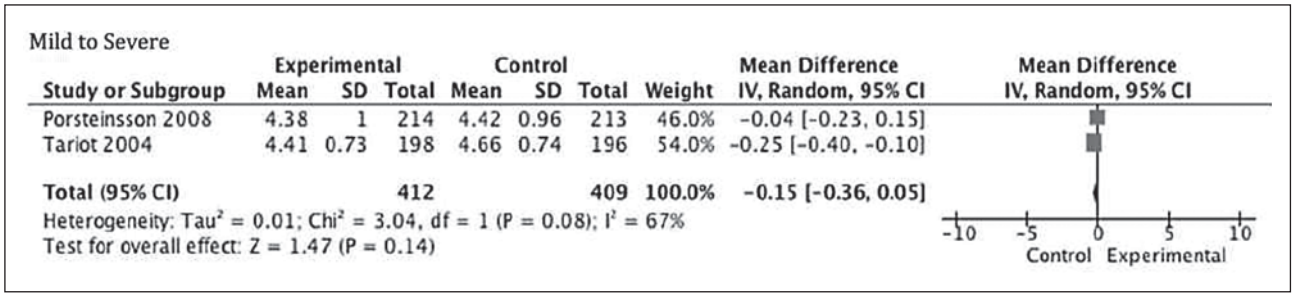

Fig. 5. Metagraph of performance on CIBIC-Plus, available from 2 studies.

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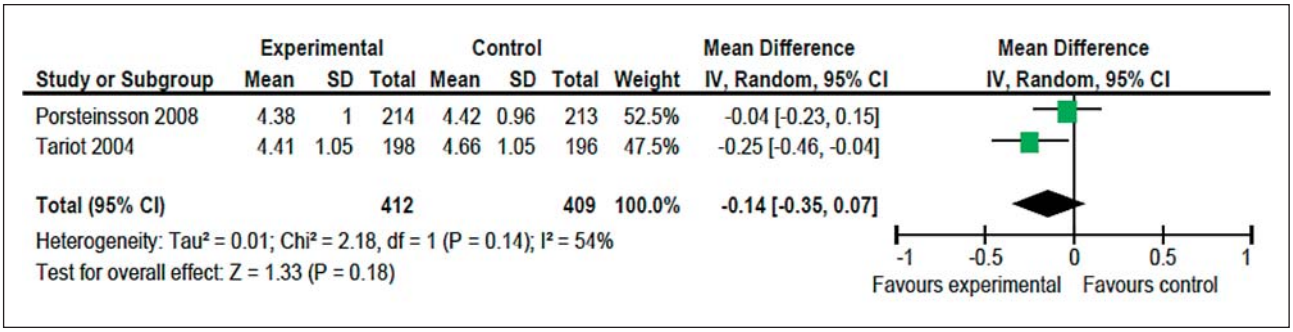
We like to present the corrected version of figure 5:



We also like to draw your attention to the fact that none of the significant methodological issues that were raised in the study by Howard et al. [3] were discussed: we are referring to the example provided in the article by Tariot [4] entitled 'Cessation of donepezil is associated with clinical decline in patients with moderate-to-severe Alzheimer's disease compared to continuation of donepezil or addition or substitution of memantine'. This data set is directly assessed with the study data provided by Tariot et al. [2] and Porsteinsson et al. [5] despite the fact that there are clear differences in the study design that, at best, make it difficult to compare these studies: as it stands, the comparisons are inappropriate. For example, the DOMINO study was a 52-week study and the others were of 24 weeks' duration. In a progressive disorder like Alzheimer's disease this difference in duration might lead to significant differences between the results of the two studies.

Another cause for concern is the inclusion of patients from all levels of disease severity in the mild-to-severe analyses. The study reported by Tariot et al. [2] included patients with an MMSE score of 5–14, which is within the approved moderate-to-severe range for which memantine is indicated. However, in the study reported by Porsteinsson et al. [5] mild patients (MMSE 10–22), for whom memantine is not indicated, are also included. A recent meta-analysis by Atri et al. [6] showed significant benefits for patients with MMSE <20 across studies that excluded the mild patient population.

We would also like to make a general comment on the confidence interval plots and suggest that most of them could be improved and rendered more informative by using another scale on the x-axis. The forest plots for figures 2, 3, and 5 should be on a different scale than those in figure 4 which have broader confidence intervals and warrant a wider range scale.

We urge the authors to reassess and amend the analysis and presentation of data in figure 5 and suggest that they revise parts of the manuscript so that they will be consistent with the corrected data. As the CIBIC-Plus endpoint is essential when assessing the efficacy of anti-Alzheimer drugs, and because the erroneously reported results may impact the discussion significantly, we respectfully suggest that an appropriate response would be to publish an erratum. As presented the incorrect data in figure 5 do not fit with the correctly stated results in the discussion section and simply confuse the reader.

Disclosure Statement

Pierre Tariot's conflicts of interest include: consulting fees from Abbott Laboratories, AC Immune, Adamas, Boehringer-Ingelheim, California Pacific Medical Center, Chase Pharmaceuticals, Chiesi, CME Inc., Elan, Medavante, Merz, Otsuka, Sanofi-Aventis; consulting fees and research support from Avanir, Avid, Bristol-Myers Squibb, Cognoptix, GlaxoSmithKline, Janssen, Eli Lilly, Medivation, Merck and Co., Roche; research support only from AstraZeneca,

Baxter Healthcare Corp., Functional Neuromodulation (f(nm)), GE, Genentech, Pfizer, Targacept, Toyama; other research support from NIA, Arizona Department of Health Services; investments: stock options in Adamas; patents: P.N.T. is listed as a contributor to a patent owned by the University of Rochester, 'Biomarkers of Alzheimer's Disease', Y.W. is employed by Wirth Consulting, a statistical consultant of Merz Pharmaceuticals GmbH, S.M.G. and M.T. are employed by the Forest Research Institute, and J.F. is employed by Merz Pharmaceuticals GmbH.

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