 doi:10.1111/j.1468-1331.2007.01713.x

LETTER TO THE EDITOR

Methodological matters on an Alzheimer's dementia trial: is a double-blind randomized controlled study design sufficient to draw strong conclusions on treatment? Reply to Dr Mazza and colleagues

S. Corrao, R. Scaglione, L. Calvo and G. Licata

Biomedical Department of Internal Medicine, University of Palermo, Italy

Correspondence: Prof Salvatore Corrao, Biomedical Department of Internal Medicine, University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy (tel.: +39 091 6552065; fax: +39 091 6552165; e-mail: s.corrao@tiscali.it).

Keywords: alzheimer's disease, dementia, multi-infarct dementia, non-alzheimer degenerative dementia

Received 2 September 2006
Accepted 23 November 2006

Sir,

We read with great interest the paper of Mazza *et al*. [1]. The aim of the study is noteworthy. Moreover, we appreciate the overall study design that represents a standard methodological approach for reaching strong conclusions on treatments. However, double-blind randomized controlled trials may have biases, confounding factors or other methodological errors. Wrong study conclusions by misleading use of statistics and other methodological matters [2] are always possible and could incorrectly influence clinician opinion and consequently spoil health-care quality. Therefore, we think a critical revision of the work of Mazza *et al*. could be useful to your readers to understand some important limitations in the study conclusions. First of all, the trial studied a small population sample and no effort to calculate sample size was made. Trials with small population samples have scare sensitivity and can bring to negative results (no differences between groups). In this case, no differences between treatment groups (Ginkgo biloba versus donepezil) could be justified by this matter. Moreover, a drop-out at follow-up ≥20% compromises the overall quality of a trial [3]. In this study, 60 patients out of 76 completed follow-up with a drop-out of about 21%. On the other hand, some considerations on the statistical analysis section are needed. ANOVA only means analysis of variance. A lot of different types of ANOVA exist. Therefore, the reader should know what kind of ANOVA was used. Moreover, outcomes were evaluated by a psychometric test (the Syndrome Kurtz test) and the Mini-Mental State Examination. Differences in resulting scores (obviously not normally distributed) should be evaluated by distribution-free (non-parametric) statistical methods like, in this case, the Kruskal–Wallis test (a non-parametric ANOVA). However, multiple comparisons between groups (when one has to manage more than two groups) need a *post hoc* evaluation test like (when applied to non-parametric ANOVA) Dwass–Steel–Critchlow–Fligner or Conover–Inman procedures [4]. This study had three groups and in no case pair-wise comparisons can be made by a *t*-test (only used if the study groups are exclusively two). For all these reasons, no statements could be made on the efficacy of the two treatments. Moreover, this study cannot evaluate tolerability of Ginkgo biloba due to the small sample size and the short-time follow-up. Having pointed out these aspects, this study has scientific value, but readers should be advised of all these considerable limitations.

References

1. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *European Journal of Neurology* 2006; **13:** 981–985.
2. Corrao S. Protective effect of smoking: misleading use of statistics. *Radiology* 2004; **233:** 934.
3. Centre for Evidence Based Medicine (UK). http://www.cebm.net/levels_of_evidence.asp (accessed 2 September 2006).
4. Conover WJ. *Practical Nonparametric Statistics*, 3rd edn. New york: Wiley, 1999.

