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Letter to the editor

Statistical considerations about the question of a selection of discriminating centres in the analysis of clinical trial. In response to the paper: "A method for controlling for a high response rate in a comparison of venlafaxine XR and diazepan in the short-term treatment of patients with generalised anxiety disorder"

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The paper of Hackett et al. takes the opportunity of a non-conclusive trial in the treatment of generalised anxiety disorder (GAD) to deal with a burning question: the heterogeneity of response among centres included in a trial, and, more precisely, the heterogeneity in the placebo response. The underlying idea is as follow. Consider a classical multicentre three-arm trial comparing a new drug, a standard drug and a placebo. Some centres will inevitably present a smaller difference between placebo and standard drug efficacy. This smaller difference may be due, in particular, to chance, to a high effect of the patient/clinician relationship that is likely to swamp the specific effect of the active drug, or to a high level of noise in the evaluations. Indeed, centres which are careless in the assessment of inclusion criteria or in the scoring of efficacy variables, will have difficulties to discriminate the placebo from the standard drug. An intuitive idea is then to discard these centres from the efficacy analysis, at least in an exploratory perspective.

The authors have followed this strategy. They have subdivided the centres according to their ability to detect a two-point difference on the HAM-A between the placebo and the standard drug and propose to analyse exclusively the data coming from the "good" centres (i.e. the discriminating centres, called *verum*-sensitive centres) when comparing the new drug to the placebo. This last analysis appears to lead to consistent statistically significant results with a 0.05 level.

Unfortunately, such an analysis inflates the type one error, and the 0.05 level is no more guarantied. Two situations may be considered to enlighten this point.

In the first situation, a "good" centre is defined as a centre that discriminates the placebo from the standard drug with a superiority of the standard drug. Imagine now a trial were the standard drug, the new drug and the placebo have the same level of efficacy (this corresponds to the "null hypothesis" of statisticians). By chance, centres will have nevertheless different levels of response in each treatment. Hence, there will still be apparently "good" and "bad" centres. "Good" centres will in fact correspond to centres for which, by chance, there is a low placebo response and/or a high standard drug response. By the way, if you compare the new drug to the placebo in the "good" centres, it will not be surprising to find the new drug artificially superior since the placebo response is, by design and in average, particularly low in these centres.

In the second situation, a "good" centre is defined as a centre that discriminates the placebo from the standard drug with a superiority either of the standard drug or the placebo. The problem presented above is no more relevant since "good" centres will correspond to centres with either a particularly high or low placebo response (same for standard drug). If you imagine, however, a trial were the standard drug is actually superior to the placebo, while the new drug is comparable to the placebo. Discriminating centres ("good" centres) will only correspond to the situation were the standard drug is superior to the placebo. By the way, the placebo response in these centres will still be biased towards a low response, and it will not be surprising to find again the new drug artificially superior.

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On a more formal point of view, this bias corresponds to an inflation of the type one error no more equal to the traditional value of 5%.

In conclusion, even if the problem of non-discriminating centres is a real problem, the solution is definitely not in the straightforward analysis of the sole discriminating centres because the statistical tests of hypothesis are no more interpretable. Some propositions have been made to deal with this issue [1], they seem to be acceptable on a statistical point of view, but are not powerful enough. Of course, enhancement of quality control procedures are a sensible methodological answer, but there is still hope in finding appropriate statistical procedures.

References

[1] Falissard B. A solution to the problem of centres with high level of measurement error in multi-centres trials with psychopharmacological treatments. Int J Neuropsychopharmacol 2002;5(Suppl 1):S197.

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