

Carta aos editores

The value of publishing negative results from a randomized controlled trial: the rosenheck's study

Mr Editor,

In the last few years, attention has been given to the problem of publication bias: it is well established that papers with negative results (when the null hypothesis is not refused) are less likely to be published in scientific journals than those with results favoring a given intervention.¹

The paper published in November 23rd, 2003 in JAMA by Rosenheck et al.² reports negative results (no differences) in randomized clinical outcomes when comparing for the comparison of olanzapine and haloperidol in combination with benzotropine for treating schizophrenia. These findings, however, do not agree with the main results of a Cochrane Systematic Review, which currently included 20 randomized controlled trials (RCTs). In this Review, olanzapine has advantages when compared to First Generation Antipsychotics in terms of clinical improvement in negative symptoms.³

In Rosenheck's trial, of a total of 4386 subjects were screened, and 2141 were eligible for inclusion, and only 309 were randomized. This restrictive inclusion enrollment process limits the generalizability of the study's findings and resulted in a sample of chronic patients with longer duration of diseases, aged 45 years in average (in olanzapine trials, the mean age of patients is around 35 years). In a more chronic population with schizophrenia it is expected that smaller differences between two treatments are to be found.⁴ Therefore, lack of statistical power could be another explanation for their negative results.

However, the critical point in this paper is a missing and simple principle: just because of chance it is expected that some trials will find no significant differences in one or more outcome measures only by chance. According to the Central Limit Theorem,⁵ it is expected that 5% of the total set of studies will find extreme results (more than two standard deviations from the mean), or 32.16% will stand beyond about one standard deviation from the actual mean.

It is crucial that high impact journals like JAMA publish trials with negative results – readers can have then a real sense about how different samples of patients (in RCTs) can produce different results. If a pharmaceutical company sponsors the trial, this is even crucial. General rules of medical statistics, such as estimations of samples, heterogeneity of populations, and the selection process, must always be considered. For the best care of individual patients, when assessing scientific information, negative results should be more than welcome by both publishers and

readers, but their conclusions need to be considered in a more comprehensive view, in the context of other similar studies.

Conflito de interesses: Maurício Silva de Lima é Gerente Médico de Neurociências do Laboratório Eli Lilly do Brasil.

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Methodological considerations on the comparison of first and second generation antipsychotics

Mr. editor,

Drs. Silva de Lima and Garcia de Oliveira Soares suggest that, in view of the large number of studies of second generation antipsychotics (SGAs) that have been conducted over the years, our finding of limited benefit for olanzapine as compared to haloperidol may be attributable to chance. This assertion rests on the assumption that all the studies of SGAs, including ours, used the same methodology. We believe that it is such methodological differences that explain the differences in results. The most revealing outcome difference between our study and the International Collaborative Trial (ICT),¹ the major study of olanzapine, is that while adherence to olanzapine was the same in both studies adherence to haloperidol was far superior in ours, almost certainly because we used prophylactic anticholinergics with haloperidol while the ICT use anticholinergics on an "as-needed" basis, for only 50% of patients.

While this could clearly explain the lack of differences in Parkinsonian side effects, could it also explain the difference in