Cognitive changes in response to antipsychotic medication: design and interpretation problems

Cognitive deficits support the best evidence of schizophrenia as a brain disease, even more so than the findings from studies on evoked potentials, regional brain volumes, cerebral metabolism and blood flow or dopamine receptor densities[1]. These deficits can be found in almost all those individuals diagnosed of schizophrenia if we consider their premorbid level[2]. They have been described before the appearance of the clinical symptoms. They are relatively independent of them and remain over a long period of time. In addition, their relationship with social-laboral functioning and with the benefit obtained from the rehabilitation programs have been previously described (for a review see)[3]. Due to all of the above, the initiatives to evaluate efficacy of the treatments, mainly pharmacological, to diminish these deficits have multiplied in recent years.

Although the general tendency is to inform on the advantages of the new antipsychotics (versus the conventional ones)[4], the studies are not exempt of the serious methodological limitations and inadequate interpretations that affect their conclusions. The relevance of these cognitive changes is, in the best of the cases, limited. There are also adequately designed studies that have reported on the absence of significant changes[5] and even worse cognitive performance after the administration of the new antipsychotics[6].

It is common to find some of these problems herein listed in prestigious journals. First, the studies that administer the same (or similar) cognitive task on several occasions tend to neglect the effects of this practice. These effects are mainly to be expected in those tests having a greater component of velocity, in those that require a way of unusual response or those that have a simple solution. In general, they suppose a potential risk in all the cognitive tasks, this making the use of control measures necessary. Secondly, the multiplication of cognitive variables makes type I error highly likely, that is, finding differences where none exist. On the other hand, recurring to one or few cognitive variables as a reflection of a brain function (or general functioning) can be equally criticized. In the third place, the previous treatments, especially in the population of patients with chronic or drug-resistant disease may condition the interpretation so that that instead of attributing the changes to the new treatment, generally unique and in doses adjusted by the research protocol, they should be attributed to the withdraw-al of the previous treatments in a group especially prone to receiving multiple medications. In the case of first episodes, the baseline evaluation is also frequently conducted after the initiation of the antipsychotics, so that the «beneficial» effects may be due to the progressive adaptation or to the regression to the mean. In the fourth place, the studies on the response of the antipsychotics have the tendency to not take other non-biological, concurrent circumstances into consideration (for example, other psychological therapies or rehabilitation or hospital discharges). Added to these problems of design and interpretation are others such as the differences in the doses, effects of the adjuvant medication, financing by laboratory companies, etc. All this assumes that the best experimental design to differentiate the cognitive effects of the antipsychotics from those of the disease itself - the placebo-controlled clinical trial - is unfeasible.

In this context, we should consider the article recently published in *Actas Españolas de Psiquiatría* by Chamorro et at.[7]. The authors attempt to check the utility of measurement of general intelligence with the Cattel «g» Factor Test to evaluate cognitive function over one year, after change to a treatment with risperidone in a group of 32 patients with several years of illness evolution. They concluded that the test «seems to be sensitive to improvement (...) of cognitive functioning» and that the treatment with risperidone «may be effective»[7]. The design they used does not make it possible to support either of these two statements, not even with its cautious writing in the conditional.

The use of the Cattel test with clinical population is very limited and adequate validation studies would be needed before considering it adequate in the population of persons with schizophrenia, both as a measure of «frontal» functioning as of general intelligence. On the other hand, due to the absence of a comparison group, the results not only do not support the fact that risperidone improves cognitive functioning in this sample, it also does not make it possible to clarify that it does not worsen it. In our experience, with a random assignment to treatments in patients who have never been treated with antipsychotics previously, risperidone was not significantly differentiated from haloperidol in its cognitive effects in the acute phase[8], after clinical stabilization[9] or after one year of treatment.

The treatment of cognitive deficits in schizophrenia will continue to be a priority in the coming years. Development of new interventions depends greatly on the rigorous evaluation of the results of the already available drug or non-drug treatments.

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Reply

We positively evaluate the reflections made by González-Blanch in their article, but we consider that we should answer some of their statements. We defend the projects that try to reach an agreement on the best neuropsychological batteries to evaluate cognitive functioning in schizophrenic patients, such as the MATRICS project[1]. We admit that the Cattell test has not been used, and thus not validated, in schizophrenic patients. That this test and not another one was chosen is because it is one of the few tests that measure the «g» factor of intelligence with demonstrated reliability and validity and because its application is easier and shorter than others. In addition, one of the reasons that motivated us to publish the study was precisely to indicate the possible use of the Cattell test and to arouse interest about its possible future validation. This is, at least, what occurred with another intelligence test that is presently used widely to measure cognitive functioning of the schizophrenic patient, such as the WAIS, whose use was initiated for this purpose without having been validated. Given its recognized utility, new forms of it continue to be validated, such as the short ones for the schizophrenic patients[2,3]. We also admit that the IQ values obtained in schizophrenic patients with the Cattell test should be contrasted with the results of the neuropsychological tests batteries to check their predictive value of cognitive functioning in these patients.

In regards to the effects of risperidone on intellectual functioning in the study patients, we indicate the final result of improvement in the IQ values measured with the Cattell test after 12 months of treatment with risperidone (without being able to know the effects of other variables that we did not control in the study) and that also correlate with the improvement in other areas, such as «clinical global impression». There are studies on the decrease of cognitive deficit of the schizophrenic patient after a treatment period with risperidone, beginning with the study of Rossi et al.[4] mentioned in our article to the most recent ones of Riedel[5], Harvey[6,7] or in our setting, that of Gurpegui[8].

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