Increasing Placebo Response in Antipsychotic Drug Trials: Let's Stop the Vicious Circle

An increasing placebo response is a major concern in antipsychotic drug trials (1–4). It has been blamed for the failure of a number of antipsychotic agents in the registration process. Currently, even standard drugs frequently fail to show superiority compared with placebo, making it difficult to prove a new drug efficacious. Several pharmaceutical companies have closed their neuroscience drug development programs, which in the end is bad for patients with schizophrenia, for whom more efficacious treatments with fewer side effects are urgently needed.

The first question clinicians may ask is why placebo-controlled schizophrenia trials are still conducted. Aren't placebo-controlled trials unethical given that effective treatment exists? The frequently encountered large placebo response is precisely the reason why the U.S. Food and Drug Administration (FDA) and the European Medicines Agency still recommend such trials. A head-to-head comparison between a new compound and an approved antipsychotic may show no difference between the two agents in a so-called noninferiority trial and make the new compound look efficacious. But it could be that neither the new drug nor the standard antipsychotic would have been more efficacious than placebo if placebo had been used as an additional comparator in the trial. Nevertheless, voices critical of the use of placebo in schizophrenia have been raised (5).

It is important to understand that placebo response is not merely a kind of a psychological effect induced by the doctor-patient relationship. Rather, the phenomenon is complex, and it is clear that methodological factors play an important role—but it is unclear which of the many potential factors explain placebo response.

In this context, Agid and colleagues (6) present, in this issue of the *Journal*, the largest and most comprehensive meta-analysis to date of the phenomenon of increasing placebo response, including all placebo-controlled antipsychotic drug trials since 1970. Their major findings are that placebo response has increased over these past few decades and that this temporal effect is explained by an increase of the number of sites per trial and by a decrease in the number of academic sites in randomized controlled trials. Furthermore, factors such as shorter trial duration, younger patients, short duration of illness, higher illness severity at baseline, and lower percentage of patients assigned to placebo (in studies published after 1997) were associated with larger placebo response, while the number of treatment arms, country, and duration of drug washout periods were not.

The main limitation of a meta-regression within a meta-analysis is that potential predictors are not consistently presented by all studies. Moreover, meta-regression is relatively insensitive, because it is based on mean values of studies. Additional analyses of individual patient data, such as those conducted by the NEWMEDS initiative (Novel Methods Leading to New Medications in Depression and Schizophrenia; www.newmeds-europe.com), are therefore important.

Agid et al. highlight their finding that the total number of sites and the number of academic sites explained the increase in placebo response over time. This finding reflects the change from single-center, university-based trials to multicenter, pharmaceutical industry-sponsored trials. Academics running clinical trials in a single center might be more interested in a positive research outcome, which might inflate drug-placebo differences. Nonacademics could be more motivated by the financial incentives and thus aim at enrolling as many patients as possible, which will increase variability and decrease drug-placebo differences.

A number of solutions are sought, including the optimization of protocols, measures to ensure the enrollment of validly acute patients, concealing the duration of the placebo run-in phase from the investigators to reduce "baseline rating inflation" (i.e., rating patients more severely ill than they actually are so that they meet the inclusion criteria), the development of more sensitive rating scales and better rater training, and the use of remote independent raters through telephone or video examinations (for a review, see reference 3). In our opinion, recruiting truly acute patients is the key issue, but current trials are so complex that in fact such patients are rarely enrolled. Many antipsychotics are available, so patients think twice before they participate in a trial, leaving the field to partially refractory patients hoping for a more efficacious drug. Consent forms are very long, and eligibility must be carefully screened, so that at the end of the process only stabilized (although still symptomatic) patients are recruited after short washout phases, turning acute-phase studies to some degree into withdrawal studies. Many participants are "professional patients" recruited by newspaper advertisements who benefit from small financial incentives.

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The use of add-on designs, an approach that is increasingly applied by the Stanley Research Foundation, could be a comparably cheap alternative to placebo-controlled monotherapy trials, although it requires that the new compound have a mechanism of action truly different from those of the current antipsychotics. Head-to-head trials proving superiority over standard antipsychotics might be another option, although this approach, even more so, requires truly more efficacious drugs. We feel that parts of the pharmaceutical industry may be blamed for focusing too long on the development of "me-too" drugs. Additional 5-HT_{2a}/D_2 antagonists seem unlikely to be breakthroughs. Indeed, parts of the pharmaceutical industry seem finally to be moving away from the development of "magic bullet" drugs that are efficacious for all symptoms of schizophrenia, moving instead in the direction of drugs that focus on a single symptom complex, such as cognitive impairment. The development of glutamatergic or nicotinergic compounds are two examples in this context.

In our recent network meta-analysis, we found that smaller trials had larger effect sizes (7). Although adjusting for trial size did not change the efficacy rank order of the antipsychotics, we need to break through a vicious circle: companies conduct large trials to assure statistical significance. The resulting large number of sites in these trials (as found by Agid et al.) does increase variability, which by definition reduces effect size. The power calculation for the next trial will suggest an even

larger sample size. This vicious circle and the various complexities mentioned above make trials extremely expensive. The National Institute of Mental Health, the FDA, the Department of Veterans Affairs, and concerned medical research agencies in other countries should fund research on drug development, including methodological innovation. Absent this, few new drugs will be developed.

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STEFAN LEUCHT, M.D.
STEPHAN HERES, M.D.
JOHN M. DAVIS, M.D.

From the Department of Psychiatry and Psychotherapy, Technische Universität München, Munich; the Psychiatric Institute, University of Illinois at Chicago, Chicago; and the Maryland Psychiatric Research Center, Baltimore. Address correspondence to Dr. Leucht (stefan.leucht@lrz.tum.de). *Editorial accepted for publication August 2013 (doi: 10.1176/appi.ajp.2013.13081129).*

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