Protocols Sought to Lower Placebo Responses

Researchers hope novel trial designs will lead to 'more efficient antidepressant drug discovery.'

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FROM THE ANNUAL CONGRESS OF THE EUROPEAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AMSTERDAM – Novel trial designs can be used to reduce the high placebo response seen in clinical trials of antidepressants and thus increase the efficiency of those trials, according to a drug development scientist who proposed a "filtering" approach at the congress.

"We have found that the response to placebo is the strongest factor in a failed clinical trial," said Dr. Emilio Merlo-Pich, of the Centre of Excellence for External Drug Discovery, GlaxoSmithKline (GSK) in Verona, Italy, who spoke at a session called "The Placebo in Psychiatry."

The placebo response trumps other reasons proposed to explain the high clinical trial failure rate for novel antidepressants, he said, including trial design features, heterogeneity of the study population, site-subject interactions, and low assay sensitivity related to clinical rating scale deficiencies.

Randomized clinical trial (RCT) outcomes can be improved by learning from past experience and using clinical databases and trial modeling, Dr. Merlo-Pich said. He and his colleagues have proposed an approach to improving RCTs using data to assess the role of recruitment centers and the problem of signal detection.

"Our study supports the implementation of prior-driven data preprocessing into RCT protocols to attenuate their failure rate, leading to a more efficient antidepressant drug discovery," he said.

A meta-analysis of 52 RCTs indicated that placebo change from baseline to the end of study strongly affects the detection of active treatment superiority (J. Nerv. Ment. Dis. 2003;191:211-8). A statistically significant positive correlation was seen between placebo response magnitude and the advantage of antidepressants over placebo (*P* less than .0001). Only 21% of antidepressant treatment arms in trials with high placebo responses (more than a 30% mean change from baseline) showed superiority over placebo, compared with 74% in trials with a lower placebo response.

Placebo responses that are 'too high' or 'too low' generate noise within a randomized clinical trial.

DR. MERLO-PICH

For the present study, a meta-analysis was conducted on nine GSK clinical trials, including 3,953 subjects with major depressive disorder, 1,197 of whom were exposed to placebo and 2,756 who had received antidepressants. The placebo response (reduction in depression score) varied highly according to the center.

A sensitivity analysis indicated that the placebo response by center was relevant for the detection of a treatment effect and for the success of the whole trial, Dr. Merlo-Pich reported. Placebo responses that are "too high" or "too low" generate noise within an RCT, he explained.

"We found that the placebo response can be so strong as to prevent any detection of a signal of pharmacologic effects, even if one is present. Therefore, the performance of each recruitment center is critical for the success of the whole trial," he said. "In spite of training, recruitment centers manage protocols differently and handle patients differently, and this introduces bias. In fact, we have found the majority of the treatment effect depends on the center's performance."

Based on the level of the placebo response, the investigators classified individual centers as "informative" or "noninformative." This classification was associated with the probability of detecting a signal of a clinically relevant treatment effect. The number of "informative" centers per study is relevant for the clinical trial outcome. "If you have enough informative centers, there is a higher probability of a positive trial," he said.

In the study, only 60% of centers in the GSK database were classified as informative based on their specific level of placebo response, he reported.

Using this information, Dr. Merlo-Pich and his colleagues then ranked the centers' performance, varying from 0 (high background noise and no chance to detect a treatment effect) to 100 (low noise and optimal condition for detecting a treatment effect). They then applied a "band-pass filter preprocessing approach" prior to statistical analysis as an enrichment strategy to single out the informative study population, reduce the noise, and improve the outcomes.

A clinical trial simulation was conducted to assess the performance of this "filtering" approach. The result was that the proportion of failed RCTs was reduced from 50% to 10%, he reported.

In implementing the model, the researchers define a-priori per-protocol high and low enrichment criteria to be applied at the end of treatment and before the statistical analysis. This identifies the noninformative centers to be eliminated, leaving the informative centers for the per-protocol efficacy analysis.

"We believe we can apply this approach to any clinical trial. This will maximize our investment and enhance patient exposure to promising new compounds," he concluded. ■

Disclosures: Dr. Merlo-Pich is a full-time employee of GlaxoSmithKline.

VITALS

Major Finding: GSK researchers have developed a "filtering" approach that will eliminate study centers with high placebo response rates and enrich the effect of active drug treatment, thus yielding more accurate results of clinical trials.

Data Source: The studies were conducted and models developed by GSK investigators.

Disclosures: Dr. Merlo-Pich is a full-time employee of GlaxoSmithKline.

Four Trials Underway

Magnetic Seizure Therapy *from page 1*

nosis of major depressive disorder and 4 with bipolar disorder. The average patient was a 50-year-old female who had had six lifetime episodes of illness, been treated with 18 medications, and been hospitalized four times, Dr. Kayser reported.

The average duration of the most recent episode of illness was 6 years in the MST group and 3.5 years in the ECT group. One out of five patients had attempted suicide.

Ten patients received ECT, and the other 10 received a full course (up to 12 treatments) of MST.

The outcome measure of effectiveness was remission or a 50% reduction in depressive symptom severity according to the Hamilton Depression Rating Scale ($HDRS_{28}$) and the Montgomery-Åsberg Depression Rating Scale (MADRS).

The two treatment groups in the study both demonstrated significant improvement over baseline. Response criteria were met by 65% of the patients, whereas 53% met the criteria for remission, Dr. Kayser reported.

The patients' mean scores on the $HDRS_{28}$ declined by approximately 12 points in each treatment arm (*P* less than .001), and on the MADRS they dropped approximately 12 points after ECT and 15 points after MST (*P* less than .001).

Several aspects of recovery from the procedure were significantly better in the MST arm, compared with ECT, she reported. "Patients were quicker to breathe independently after anesthesia, and their reorientation time was faster, based on their answers to biographical questions such as name, date, and so forth," she said.

Compared with their ECT counterparts, MST patients were quicker to breathe independently after anesthesia, and their orientation time was faster, based on answers to biographical questions.

Mean recovery time (defined as independent breathing) was nearly 4 minutes after ECT, compared with approximately 1.5 minutes with MST (*P* less than .01).

Reorientation time was 8 minutes vs. 2 minutes (*P* less than .01). EEG showed no effects on brain structure with either approach.

Neither arm showed significant changes in cognitive outcomes, including learning and memory (verbal and visual), abstract knowledge, executive functions (verbal fluency), and speed of processing.

This is an emerging treatment for severe depression that is being studied in only four clinical trials that are centered in New York/Dallas; Australia; Bonn, Germany; and Berlin. ■

VITALS

Major Finding: This was one of only a few clinical studies of MST. It found comparable outcome to ECT but quicker recovery and reorientation.

Data Source: Prospective study of 20 patients: 16 with major depressive disorder and 4 with bipolar disorder.

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