Considering the Complexity of Treatment Response in Psychiatric Clinical Trials

To the Editor: In a recent issue of *JCP*, Issari and colleagues[1] demonstrated that significant improvement of obsessive-compulsive disorder (OCD) could be observed within the first 2 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs). This finding is an essential contribution to the field and provides further support to previous research published by our group. We reported that improvement of OCD observed after 4 weeks of treatment with an SSRI was a strong predictor of outcome[2] after 12 weeks of pharmacotherapy. Given the traditional assumption that treatment response in OCD is delayed for several weeks and that therapeutic shifts should not be considered early in the course of treatment,[3] these findings may represent a paradigm shift in OCD treatment.

Nonetheless, we would like to shed light on other factors that could explain such an early improvement. Issari and colleagues state that mechanisms attributed to the pharmacologic action of SSRIs account for the observed rapid gain, since a significant difference between the active and placebo arms was evident as early as week 2. However, there could be other phenomena contributing to the early response that cannot be disregarded despite the differences between the active and placebo arms.

In all studies included in their meta-analysis, inactive placebo pills were used. Active placebos, which are able to yield perceived side effects, have been associated with higher placebo responses than inactive pills. Consequently, although the placebo effect operated in both arms, its magnitude in each arm was not equal. In the SSRI group, it may have contributed to the outcome in a higher degree than in the placebo group, since the presence of side effects can result in a higher expectancy of improvement.[4] This leads us to consider that further investigation of the components of the placebo effect should not be regarded as a minor issue.

Indeed, there has been a contemporary reduction of the difference between active and placebo arms in pharmacologic studies of different mental disorders, including depression,[5] mania,[6] and OCD.[7] This reduction cannot be completely explained by a diminished response to the active drug, but rather to an increase in the placebo response. Therefore, it became harder to disentangle the direct pharmacologic effects of a drug from the range of different phenomena that account for the so-called "placebo effect."

Tempting as it may be to attribute the difference between the drug and placebo arms solely to the direct effects of the pharmacologic agents, there may be more for us to learn about that difference. Accepting the challenge to acknowledge the components of the placebo response as inherent to treatment, regardless of the use of active drugs, may be essential for increasing the success of our current treatment options. Future trials are needed to challenge the 12-week timeframe established as the optimal duration of an SSRI trial for OCD and to fill relevant gaps in the OCD-treatment literature, such as how to boost initial treatment response and how to manage additional interventions to avoid poor outcomes in individuals who fail to achieve early improvement with SSRI treatment.

The corresponding author of the article discussed in this letter was shown the letter and declined to comment.

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