

It is illegal to post this copyrighted PDF on any website.

Considering the Complexity of Treatment Response in Psychiatric Clinical Trials

To the Editor: In a recent issue of *JCP*, Issari and colleagues¹ 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 outcome² 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.

REFERENCES

1. Issari Y, Jakubovski E, Bartley CA, et al. Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis. *J Clin Psychiatry*. 2016;77(5):e605–e611. 10.4088/JCP.14r09758
2. da Conceição Costa DL, Shavitt RG, Castro Cesar RC, et al. Can early improvement be an indicator of treatment response in obsessive-compulsive disorder? implications for early-treatment decision-making. *J Psychiatr Res*. 2013;47(11):1700–1707.
3. Koran LM, Hanna GL, Hollander E, et al; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2007;164(suppl 7):5–53.
4. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull*. 2004;130(2):324–340.
5. Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. *Neuropsychopharmacology*. 2012;37(4):851–864.
6. Welten CC, Koeter MW, Wohlfarth T, et al. Placebo response in antipsychotic trials of patients with acute mania: Results of an individual patient data meta-analysis. *Eur Neuropsychopharmacol*. 2015;25(7):1018–1026.
7. Ackerman DL, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2002;22(3):309–317.

Juliana Belo Diniz, MD, PhD^a

julianadiniz@usp.br

Roseli Gedanke Shavitt, MD, PhD^a

Eurípedes Constantino Miguel, MD, PhD^a

Daniel L. C. Costa, MD^a

^aDepartment and Institute of Psychiatry, University of Sao Paulo Medical School, Sao Paulo, Brazil

Potential conflicts of interest: Dr Shavitt received a travel grant from Lundbeck. The remaining authors of this letter declare that they have received no personal financial support from private companies in the last 12 months. Studies conducted by the authors have received financial support in the form of grants provided by the following Brazilian governmental agencies: the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, National Council for Scientific and Technological Development, Brasília, Brazil; Grant nos. 573974/2008-0, 521369/96-7, and 475919/2006-8) and the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, São Paulo Research Foundation, São Paulo, Brazil; Grant nos. 2005/55628-08, 2006/50273-0, 2008/57896-8, and 2011/21357-9).

Funding/support: None.

J Clin Psychiatry 2016;77(12):e1652
dx.doi.org/10.4088/JCP.16lr11057

© Copyright 2016 Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.