Published in final edited form as:

Pain. 2008 October 15; 139(2): 479–480. doi:10.1016/j.pain.2008.07.027.

Role of Placebo Factors in Clinical Trials with Special Focus on Enrichment Designs

Roland Staud¹ and Donald D. Price²

¹Department of Medicine, McKnight Brain Institute, University of Florida, Gainesville, Florida 32610

²Department of Oral Surgery, McKnight Brain Institute, University of Florida, Gainesville, Florida 32610

Keywords

Pregabalin; Enrichment Designs; Fibromyalgia; Chronic pain; Study Design

“We dance around the circle and suppose, while the secret sits in the center and knows.” ---
Robert Frost

We appreciate Dr. Moore and colleagues' comments, but think that there is nothing convoluted or mythical about placebo effects. On the contrary such effects can be precisely measured and many of their neurobiological underpinnings are well understood. Despite enormous variance among clinical trials and probably also within clinical practice, placebo effects exist and have bedeviled outcomes of research studies for decades. For example, our meta-analysis of 23 clinical analgesic studies designed to measure placebo effects showed some of these effects to be moderate to strong (Cohen's *d* of 0.5 or greater) [6]. In this context it is important to note that magnitude estimates of placebo effects require an untreated natural history condition for comparison with the placebo, something that the vast majority of clinical trials, including the FREEDOM trial [1] did not do.

In our recent editorial [4] we voiced concern that the study design (Enriched Enrollment with Randomized Withdrawal) used for FREEDOM could have inflated pregabalin's long-term effectiveness on fibromyalgia (FM) pain. For example, expectations and thus placebo effects may have become very powerful after an open-label run-in phase which may have contributed to unblinding of patients as well as investigators. To control for the potential presence of such placebo factors the FREEDOM investigators used a complex strategy of censoring those patients whose drug allocation concealment may have been compromised by cues like more pain or adverse reactions. Most notably, they censored patients who experienced the two most common pregabalin side effects, dizziness and somnolence. Although this resulted in the elimination of many patients from the double blind phase, there were many other drug related effects (16 at least) and possibly others that could have served as cues for the active study drug. As we pointed out in our editorial [4], no single side effect by itself needs to serve as the cue

© 2008 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Corresponding author: Roland Staud, M.D., Department of Medicine University of Florida College of Medicine, Gainesville, FL 32610-0221, Telephone: (352) 273-5346, Fax: (352) 392-8483, Email: staudr@ufl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

for the subjective identification of the active drug. All that is required is that the different conditions of the study, pregabalin versus placebo, can be subjectively distinguished. In this regard, it is notable that no attempt was made to monitor blinding, either of investigators or patients.

Monitoring of the study blind could have easily been accomplished, given what we now know about proximal mediators of placebo responses [3;7]. Having a placebo group in a study only controls for the placebo effect—it does not measure it. Since most drug trials, including the FREEDOM, do not measure expectations and desires for pain relief, these studies miss the opportunity to assess relevant factors that drive placebo effects. It is feasible to measure these factors that are predictive of the variability of placebo responses in all groups within a study. Importantly, the contribution of these factors can even be assessed in groups receiving the active treatment (like the pregabalin group) and not just the placebo.

In their response to our editorial in PAIN, Dr. Moore and colleagues comment that enrichment designs do not seem to affect the number of $\geq 50\%$ treatment responders in FM and neuropathic pain trials [5]. In particular, they argue that in the published FM trials the NNT was 3.8 after three months for a maximum titrated dose of 600 mg pregabalin daily which was similar to FREEDOM, where the calculated NNT was 3.4 for 600 mg daily. Besides the fact that only FREEDOM and not the randomized controlled FM trial [2] used 600 mg of pregabalin daily, *both studies employed enrichment designs*. This lack of relevant comparisons seems to invalidate their conclusions that enrichment designs had only negligible effects on study outcomes. Thus the validity of enrichment designs in clinical trials will require further study, in particular the careful assessments of placebo factors.

References

1. Crofford LJ, Mease PJ, Simpson SL, Young JP, Martin SA, Haig GM, Sharma U. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-months, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008;136:419–431. [PubMed: 18400400]
2. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, Lamoreaux LK, Martin SA, Sharma U. Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:1264–1273. [PubMed: 15818684]
3. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008;59:565–590. [PubMed: 17550344]
4. Staud R, Price DD. Long-Term Trials of Pregabalin and Duloxetine for Fibromyalgia Symptoms: How Study Designs Can Affect Placebo Factors. *Pain* 2008;136:232–234. [PubMed: 18384959]
5. Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrolment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *Br J Clin Pharmacol*. 2008in press
6. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2002;99:443–452. [PubMed: 12406519]
7. Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients - An empirical investigation. *Pain* 2003;105:17–25. [PubMed: 14499416]