Published in final edited form as:

Pain. 2008 August 31; 138(2): 474. doi:10.1016/j.pain.2008.07.016.

Importance of Measuring Placebo Factors in Complex Clinical Trials

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 regret the typo and acknowledge that the open label run-in phase of the FREEDOM trial lasted 6 weeks [1]. However, we continue to have concerns regarding the validity of data obtained by FREEDOM using an Enriched Enrollment with Randomized Withdrawal (EERW) study design as described in our previous editorial [4]. While this approach may be efficacious clinically, we do not think that sensitivity analyses as suggested by Dr. Crofford, will overcome the problem that prior exposure to an experimental treatment in an open label qualification phase may invalidate drug-placebo comparisons made during a later randomized, double-blinded phase. Because in enrichment designs, the same patients are exposed to several drug and non-drug conditions, the probability of detecting the drug condition becomes enhanced, particularly through drug withdrawal effects that may be very different from the drug's side effects. These concerns are particularly relevant because of the relatively rapid pregabalin taper used in the placebo group. Most importantly, placebo effects may have inflated the responder analysis. Any cues, no matter how subtle, may increase the somatic focus of study participants, a factor that has been shown to play an important role for placebo effects [2;3]. Thus true drug effects may have been magnified by placebo related factors, including expectations and conditioning.

We think that sensitivity analyses as done in the FREEDOM trial are unlikely to resolve these concerns because no single effect, side effect, or withdrawal symptom may account for problems related to EERW trials. All that is required is that the overall profile of symptoms and side-effect changes provide sufficient cues for patients to notice that they are still receiving or no longer receiving the study medication.

Although our comments are not meant to imply that pregabalin does not have any long term efficacy for FM pain, we would like to emphasize that only direct measurement of placebo

© 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.

factors, including patients' expectations and verification of allocation concealment will allow precise estimates of true treatment effects.

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. Geers AL, Helfer SG, Weiland PE, Kosbab K. Expectations and placebo response: A laboratory investigation into the role of somatic focus. *Journal of Behavioral Medicine* 2006;29:171–178. [PubMed: 16374671]
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]