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Long-Term Trials of Pregabalin and Duloxetine for Fibromyalgia Symptoms: How Study Designs Can Affect Placebo Factors

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The results of two 6-months long, randomized, double-blind, controlled trials (RCT) of the anticonvulsant pregabalin (Crofford et al., 2008) and the balanced serotonin-norepinephrine re-uptake inhibitor (SNRI) duloxetine (Russell et al., 2008) are published in this issue of PAIN. While these studies were designed to generate safety and efficacy data for two new fibromyalgia (FM) medications they used very different trial designs to achieve these goals. In the duloxetine study effectiveness for FM symptoms was measured through improvement of primary and secondary endpoints, including pain. In contrast, the pregabalin trial used group membership ($\geq 30\%$ pain reduction) after 6 months as a surrogate measure of effectiveness. In this editorial we propose that factors contributing to the placebo effect, likely affected each trial differently. Medication side-effects could easily have biased each trial through cues that signaled the presence of the active drug condition. In the duloxetine study, placebo effects may have been minimized by terminating patients with early adverse events/side effects or inflated by the remaining difference in side effect profiles between the two groups. However, because of its unusual enrichment design, the pregabalin study may not only have compromised its allocation concealment but also inflated the difference between pain levels across placebo and active treatment groups by factors now known to generate placebo effects (Price et al., 2008).

Classical Trial Design Used for the Duloxetine Trial

As presented in this issue of PAIN, the RCT of duloxetine represents an example of how currently most Phase III clinical trials are conducted. This study of FM patients evaluated multiple relevant endpoints, as required for FDA registration. Similar to a previous study (Arnold et al., 2005), duloxetine's effects on FM symptoms were independent of concurrent depression. The results of the current trial are consistent with previously reported benefits of other anti-depressants for FM symptoms, like amitriptyline (Carette et al., 1994) or milnacipran (Vitton et al., 2004).

The design of the duloxetine study closely followed the traditional model for RCTs which represents the current gold-standard for clinical drug testing. As in every trial, however, drug

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specific effects and side-effects can compromise allocation concealment and may alter expectations of the study participants resulting in treatment expectations that can positively or negatively impact relevant trial outcome measures. Thus Duloxetine's side-effects could have influenced the outcome of the trial in either direction.

However, positive effects on trial outcome measures become much more likely, when enrichment designs are used to ascertain a medication's effectiveness, as described below. We suggest that such an unusual study design strongly favors the placebo effect, like in the case of the pregabalin trial, thus exaggerating the short and long-term effectiveness of this drug.

Enrichment Design Used for the Pregabalin Study

Pregabalin has been approved by the FDA as effective therapy for painful diabetic neuropathy, postherpetic neuralgia and more recently for FM. Pregabalin's modulation of presynaptic voltage gated calcium channels seems to be the major mechanism by which this drug reduces the well known central hyperexcitability and chronic pain associated with these chronic pain syndromes (Dworkin et al., 2003; Lesser et al., 2004; Crofford et al., 2006; Arnold et al., 2007; Mease et al., 2008). Additional long-term trial data of pregabalin for FM symptoms are presented in the current issue of PAIN (Crofford et al., 2008). Because of its unusual enrichment design, we think that this study provides long-term safety data of multiple pregabalin dosages in a large patient group, but it was unable to deliver convincing evidence for long-term efficacy of this drug in FM.

This study of pregabalin for FM symptoms used a well known enrichment design wherein investigators selectively used drug responders ($\geq 50\%$ improvement of FM symptoms and self improvement rating of better than "minimally improved") from a two week open label run-in phase in the subsequent double blinded placebo controlled trial. For this purpose FM patients had their daily dose of pregabalin titrated to the most effective and side effect free level during the open-label part of the trial. This was followed by a six months blinded period during which about half the FM patients were maintained on their individual dose of the study drug while all others were switched to placebo on a random basis. The study endpoint was the number of participants retaining more than 30% reduction of their FM symptoms after six months.

Inherent Problems with Enrichment Designs and their Relationship to Placebo Effects

This enrichment design was meant to explore the long term efficacy of pregabalin for FM symptoms in treatment responders using the surrogate endpoint of group membership. At first glance this approach appears advantageous because it seems to reflect precisely what a skilled physician would do in clinical practice, i.e. titrate patients to the most effective dose and if successful, subsequently maintain only treatment responders on the drug.

While this approach may be efficacious clinically, we would like to provide several reasons why such enrichment designs may fail to do what they are intended to do [see also (Leber and Davis, 1998)]. Our overall point is that the prior exposure to an experimental treatment in an open label (OL) qualification phase may invalidate drug-placebo comparisons made during a later randomized, double-blinded (DB) phase. The lower treatment effects in the placebo control group may be inflated by adverse effects related to drug withdrawal, chance (i.e., some "responders" coincidentally have reduced symptoms at the time of testing), and most critically, the breaking of the blinded condition. In enrichment designs, the same patients are exposed to several drug and non-drug conditions, thereby enhancing the probability of detecting the drug condition wherein side effects are more prevalent as well as the placebo condition wherein a decline in side effects and increase in drug withdrawal effects could occur. These multiple

factors can contribute to mistaken estimates of the difference between drug and placebo conditions. Importantly, no single side effect or withdrawal symptom may account for this problem by itself. All that is required is that the overall profile of symptoms and side-effect changes provides sufficient cues for patients to notice that they are still receiving or no longer receiving the study medication.

How then did the investigators deal with this important issue? They only designated side-effects as adverse events (AE) during the 6 months DB if they were new and not reported during the OL phase or events that worsened during the DB. No mention was made of individuals whose side effects diminished during the DB. Because at least one third of pregabalin treated patients had drug specific AEs, like dizziness, somnolence, and headaches during the OL phase, persistence or disappearance of these AEs during the DB phase may have effectively removed blinding of patients as well as investigators.

These problems interact with problems long known to be inherent in placebo conditions. Many of the conditions necessary to achieve adequate control for the placebo effect are not satisfied in studies of pain treatments wherein the active treatment can be subjectively distinguished from the control treatment. Examples of this problem abound in the literature on complementary alternative medicine and in pharmacological studies of analgesic agents that have perceptible side effects. What is needed are alternative ways of assessing and controlling for placebo effects and these potential alternatives may be integrally related to an increased understanding of mechanisms of placebo analgesia. For example, studies have identified factors that contribute to placebo analgesia, including expected benefits, beliefs about the agent that is administered, and level of desire for pain reduction (for review see Price et al., 2008). These factors have been shown to account for a large amount of variance in post-treatment pain ratings and in placebo responses. It has been proposed that measuring these factors could be an alternative method of assessing the contribution of placebo factors that occurs within the active treatment condition as well as within the placebo condition (Price et al., 2008).

The interpretation of group separation in the pregabalin study is quite difficult if not impossible. The most important question is whether these results really mean that pregabalin remained effective for FM symptoms in more than 50% of the treatment responders over more than half a year. Unfortunately, this trial was unable to answer this question mostly because of problems that we have already described. Placebo effects that are embedded within an active treatment could have been assessed by measuring the contributions of placebo-related factors to symptom improvement. This approach could have helped to determine the long-term efficacy of pregabalin in FM.

Two recent acupuncture studies for different painful conditions, such as migraine, tension-type headache, chronic low back pain, and osteoarthritis, measured the contribution of placebo factors on study outcomes (Bausell et al., 2005; Linde et al., 2007). Both studies found that ratings of expected benefits but not group assignment predicted therapeutic outcome. They represent examples of how explicit measurements of placebo factors within clinical trials can be used to determine how much of the therapeutic effect can be attributed to placebo. These factors include ratings of expected improvement and answers to the following question: "Which treatment group do you think you belong to?"

Conclusions

Some of the ambiguities related to effects of treatment studies, like those discussed in this editorial, can be removed by measuring factors that induce the placebo effect and by verifying allocation concealment. These measurements could take place at multiple time points during the trial in order to monitor placebo contributions over time and the maintenance of the blind

(Linde et al., 2007; Price et al., 2008). This will result in better estimates of “true” treatment effects which will not only be of great relevance for patients and health care providers but also for regulatory agencies.

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References

- Arnold LM, Goldenberg DL, Stanford SB, Lalonde J, Sandhu HS, Keck PE, Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007;56:1336–1344. [PubMed: 17393438]
- Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 2005;119:5–15. [PubMed: 16298061]
- Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Eval Health Prof* 2005;28:9–26. [PubMed: 15677384]
- Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. *Arthritis Rheum* 1994;37:32–40. [PubMed: 8129762]
- 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(please add volume and pages)
- Crofford LJ, Simpson S, Young JP, Haig G, Sharma U. A Six-month, Double-blind, Placebo-controlled, Durability of Effect Study of Pregabalin for Pain Associated With Fibromyalgia. *Arthritis Rheum* 2006;54:L44.
- Dworkin RH, Corbin AE, Young JP, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia - A randomized, placebo-controlled trial. *Neurology* 2003;60:1274–1283. [PubMed: 12707429]
- Leber PD, Davis CS. Threats to the validity of clinical trials employing enrichment strategies for sample selection. *Control Clin Trials* 1998;19:178–187. [PubMed: 9551282]
- Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy - A randomized controlled trial. *Neurology* 2004;63:2104–2110. [PubMed: 15596757]
- Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B, Willich SN, Melchart D. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 2007;128:264–271. [PubMed: 17257756]
- Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP, Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol*. 2008in press
- 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]
- Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MD, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008(please add volume and pages)
- Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol* 2004;19:S27–S35. [PubMed: 15378666]