Pain 138 (2008) 479–483

PAIN

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Topical review

# Placebo response in neuropathic pain trials ☆

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Received 26 June 2008; accepted 30 June 2008

## 1. Introduction

Variability in response to "placebo" complicates the design and interpretation of clinical trials. Clinical trials of antidepressants for major depression have been plagued by high placebo responses across clinical trials with the same drug and substantially similar designs. In some cases, placebo response rates have been as high as 50–70% [5,29]. As with outcome measures in depression, pain intensity and pain relief are highly subjective constructs and clinical trials of analgesics are also associated with high and variable placebo responses [12]. Because neuropathic pain appears to be less responsive to treatment, this type of pain has been considered less susceptible to placebo response (or to less extreme variability). However, recent experience in large randomized parallel group placebo-controlled trials in neuropathic pain seems to indicate otherwise [10].

The purpose of using a placebo control in clinical trials is to establish internal sensitivity of the trial to distinguish a true treatment effect from other factors that contribute to a response (generically referred to as "the placebo response"). These influences include expectation, conditioning, regression to the mean and environmental factors including random effects. It has generally been thought that an initial placebo response stabilizes after a number of weeks and that longer term trials should establish a lasting treatment effect beyond placebo response [5,25]. Regulatory agencies, such as FDA and EMEA, require studies of 12-weeks duration for chronic pain, such as neuropathic pain, to demonstrate the durability of response. Furthermore, this duration of exposure needs to be at the target dose. For many drugs that are potential analgesics, an acclimatization period is needed to overcome tolerability (e.g., CNS) or other safety issues (e.g., toxicity with opioids) at the ultimate effective dose. The need for a post-randomization, double-blinded titration phase to reach a target dose can add many weeks to the duration of the trial. Clinical trial designs for gabapentin, pregabalin and duloxetine have accomplished attainment of target doses in a short period of time (usually 1 week or less). However, trials of topiramate, lamotrigine, oxcarbazepine and lacosamide have incorporated slow titration periods of 4–10 weeks resulting in total trial durations of 16–22 weeks. These longer duration trials are instructive for examining placebo response over an extended period of time.

We reviewed a number of studies in neuropathic pain with emphasis on long-term trials >12 weeks to asses the magnitude and time-course of the placebo response in randomized, parallel group placebo-controlled trials. This was not a systematic review. Only trials of oral treatment were considered. Trials of duration <4 weeks, crossover trials, trials that used 'active' placebo, or small trials with fewer than 30 subjects assigned to placebo were all excluded from consideration. A primary pain endpoint based on change from baseline using NRS (numeric rating scale) or VAS (visual analog scale) measures was required. The emphasis was on clinical trials that were intended to meet the stated goals of

☆ This paper includes material presented in part at the 10th Mechanisms and Treatment of Neuropathic Pain conference, Snowbird Utah, November 3, 2007.

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doi:10.1016/j.pain.2008.06.024

Table 1
Responses to placebo in randomized, double-blind parallel design trials in neuropathic pain

| Drug | Placebo group sample size | Endpoint week | Mean % change from baseline* | Proportion of responders (⩾50% pain reduction) | Proportion discontinuing for lack of efficacy | Ref. |
|---|---|---|---|---|---|---|
| Lamotrigine-30004 | 85 | 19 | 35% | 27% | n/a | [28][a] |
| Lacosamide-614 | 59 | 10 | 34% | n/a | 6.8% | [16] |
| Duloxetine HMAW | 116 | 12 | 33% | 26% | 3.5% | [8][b] |
| Topiramate-003 | 126 | 18 | 32% | n/a | 21% | [25] |
| Oxcarbazepine | 70 | 16 | 31% | n/a | 4.3% | [9] |
| Pregabalin-040 | 81 | 8 | 29% | 30% | 11.1% | [cd] |
| Topiramate-002 | 119 | 22 | 28% | n/a | 24% | [28] |
| Lacosamide-768 | 64 | 18 | 27% | 27% | 3.1% | [e] |
| Oxcarbazepine | 89 | 16 | 27% | n/a | 5.6% | [2] |
| Duloxetine | 116 | 12 | 27% | 30% | n/a | [14] |
| Pregabalin-149 | 97 | 12 | 27% | 30% | 11.5% | [26][c] |
| Venlafaxine | 81 | 6 | 27% | 34% | 6.3% | [21] |
| Lamotrigine-30005 | 84 | 19 | 26% | 23% | n/a | [28][a] |
| Topiramate-001 | 136 | 22 | 25% | n/a | 20% | [25] |
| Lacosamide-742 | 90 | 18 | 24% | 24% | 2.2% | [f] |
| Duloxetine HMAV | 108 | 12 | 24% | 27% | 4.6% | [30][b] |
| Pregabalin-029 | 97 | 5 | 23% | 18% | 2.1% | [11][c] |
| Lacosamide-743 | 74 | 18 | 23% | n/a | n/a | [g] |
| Topiramate | 109 | 12 | 22% | 21% | 14.6% | [15] |
| Gabapentin | 81 | 8 | 22% | n/a | 6.2% | [1] |
| Pregabalin-014 | 85 | 6 | 20% | 15% | 1.2% | [18][c] |
| Oxycodone | 77 | 6 | 22% | n/a | 14.3% | [7] |
| Pregabalin-131 | 70 | 8 | 11% | 15% | 4.3% | [19][c] |
| Gabapentin 9451008 | 189 | 14 | n/a | 24% | 2.1% | [d] |
| *PHN* | | | | | | |
| Tramadol | 63 | 8 | 44% | 22% | n/a | [3] |
| Pregabalin-81004 | 90 | 4 | 25% | 18% | 4.4% | [d] |
| Pregabalin-127 | 84 | 8 | 17% | 20% | 7.1% | [4][cd] |
| Gabapentin | 111 | 7 | 16% | 14% | 3.6% | [17] |
| Pregabalin-030 | 88 | 5 | 15% | 17% | 2.3% | [cd] |
| Pregabalin-196 | 93 | 13 | 10% | 8% | 23.7% | [27][c] |
| Gabapentin | 116 | 8 | 8% | n/a | 2.3% | [20] |
| Pregabalin-045 | 81 | 8 | 4% | 10% | 8.6% | [22][c] |
| *Mixed* | | | | | | |
| Lamotrigine-30010 | 109 | 14 | 33% | 36% | 6.3% | [24][a] |
| Pregabalin-155 | 65 | 12 | 24% | 24% | 29.2% | [6][c] |
| Gabapentin | 152 | 8 | 14% | 14% | 3.3% | [23] |

* The mean percentage change from baseline is reported if available, else the ratio of the mean change from baseline over the mean baseline score is reported as a percentage.

[a] Available at http://ctr.gsk.co.uk/Summary/lamotrigine/studylist.asp (accessed 13 May, 2008).

[b] Available at http://www.lillytrials.com/results/by-product/results_cymbalta.html (accessed 13 May, 2008).

[c] Lyrica European Public Assessment Report, 2004. Scientific discussion. Available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/084504en6.pdf (accessed 25 Jan., 2008).

[d] Gabapentin and pregabalin trials available at http://www.clinicaltrials.org/search/ (accessed 13 May, 2008).

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international regulatory agencies and were consistent in design features, endpoints, analysis plans and patient selection criteria. Most clinical trials summarized here were in painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN) populations.

## 2. Magnitude of placebo response

Table 1 shows the magnitude of the placebo response for the studies reviewed in terms of percentage reduction in pain score from baseline to study endpoint, proportion of responders with at least 50% reduction in pain

score from baseline at study endpoint and proportion of the population who discontinued for lack of efficacy. Mean pain score reduction ranged from 4% to 44% across all studies. In the PDN population the median magnitude of placebo response was 26% (weighted mean in the 5 trials of 12-week duration ($n = 546$) was 27%; range across all trials was 11–35%). For comparison, the median was 15–16% across all studies in the PHN population. However, the range of responses was a surprisingly wide 4–44%, as the placebo response has generally been thought to be low and more consistent between trials, although the range was skewed by 1 trial conducted within France. For studies with a mixed neuropathic pain population, the result was in between PHN and PDN, probably reflecting the fact that the majority of the population in these studies have PDN. The sample size in the placebo arms of these trials should be sufficient to reflect the true average placebo response but the variability from one trial to another was still very large.

## 3. Variability of placebo response throughout the time-course of a trial

Fig. 1(A) shows the time-course of placebo response throughout the treatment period for the 17 trials in PDN, in which change from baseline data by time point was available. There was wide variability in response at each time point between trials and in many trials there was no indication that the placebo response was reaching a plateau even by 19 weeks. Trials conducted by the same sponsor (and in several cases contemporaneously and with identical designs) were no more consistent in placebo response than other trials.

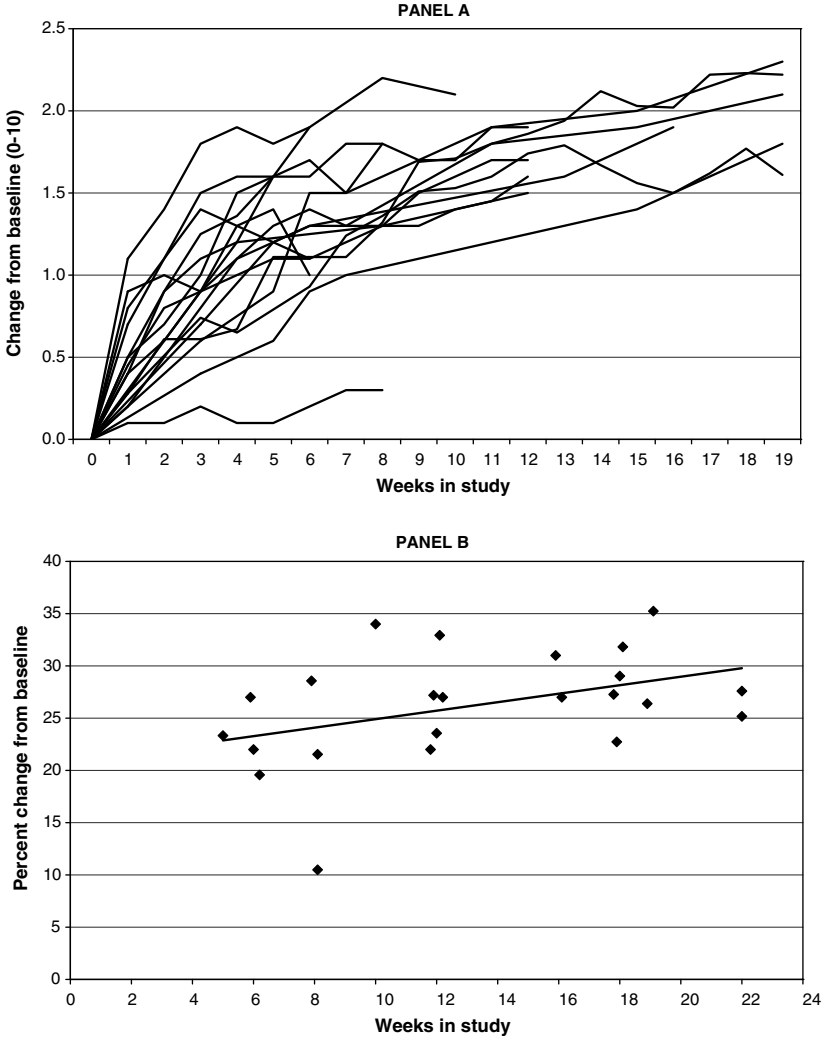


Fig. 1. Placebo response over time in study. (A) Change from baseline pain score (0–10) at time points over trial duration for 17 diabetic neuropathic pain trials for which datapoints were available. Actual data from sponsors were used if available else points were estimated from graphical presentations. VAS (0–100) scores were converted to a 0–10 scale. (B) Placebo response at study endpoint (for ITT, LOCF analyses) plotted against the duration of trial for the diabetic neuropathic pain trials listed in Table 1. The simple regression (solid line) indicates a trend for greater placebo response as trial length increases.

## 4. Variability in placebo response by the duration of trial treatment period

Fig. 1(B) shows the endpoint percentage pain score reduction data for PDN trials from Table 1, displayed by duration of the study. For a study of any given duration there is wide variability in magnitude of response range. There was a weak tendency for the placebo response to be greater in magnitude for longer term studies than in shorter term studies. If real, this has significant ramifications for designing long-term parallel design placebo-controlled trials of the type likely to be required for the approval of new treatments for neuropathic pain. The number of treatment arms ranged from 2 to 4 in these trials and although those with 4 arms appeared to have greater placebo response, these were also the trials with the longest duration, and the range of responses was wide and near overlapping. There was no obvious difference in those studies ($n = 9$) using prolonged titrations compared with those without titration phases.

## 5. Has the placebo response changed in recent years?

The placebo response was evaluated by year in which the trial was reported to be initiated (for 6/24 trials this information was not available and it was assumed to be 3 years prior to submission for publication). The trials were conducted between 1996 and 2006. Across all PDN trials, there was a tendency for increasing placebo response since 1996 but if the response was corrected for the duration of trial there was no tendency for a change over time. In fact, in the 5 trials of 12-week duration, if anything, the placebo response decreased in more recent trials. This finding appears to be in contrast to observations of a drift toward increasing placebo response in more recent trials in depression [29].

## 6. How can the placebo response be managed?

Clearly, on average, the patients assigned placebo do well just by being in a clinical trial – pain scores were reduced substantially, a reasonable number of participants met an accepted definition of responder and very few elected to drop-out of the study for lack of efficacy. This is good for subjects but a problem for designing a study to separate test drug from placebo. Much has been written about factors that may underlie success in separating drug response from placebo, including use of a placebo run-in period, discontinuation of prior analgesic treatments, flexible dosing rather than fixed dose assignments, exclusion of subject with mild pain at baseline and specificity of the pain score instrument [10,25,28]. Attempts to incorporate a single-blind placebo run-in period to cull out 'placebo responders' before starting the test drug have not been very successful. The strategy of eliminating all analgesic use prior to randomization thus far has only a slight beneficial impact on successful outcome [10] and presents ethical issues in those subjects to be randomized to placebo for a prolonged period of time. The fact is that the practical implementation of the large trials required to support the approval of drugs in chronic pain indications requires multicenter trials conducted in a diverse range of countries and cultures with unknown and probably uncontrollable expectations. In an analysis of placebo response in mostly acute pain trials, McQuay concluded that the largest determinant of placebo response is related to random factors [12]. It would therefore appear that trying to suppress the placebo response in a long-term parallel design seems counterproductive or even futile, especially if a blinded titration period is required and if drop-outs from the trial are considered as treatment failures. Do we need to design trials differently? Classical multi-period crossover trials have been attractive because of sample size efficiency. However, if each treatment period needs to be 12 or more weeks in each cycle, the analysis becomes problematic if diminishing numbers of subjects complete all periods in the trial and drop-outs are analyzed as treatment failures. Trials of drugs for the treatment of psychiatric disorders have successfully used the randomized withdrawal design. In this circumstance, the benefits of being in a clinical trial and the 'placebo' effect are put to good use such that subjects achieve maximum pain relief from open-label drug prior to randomization and then the durability of a true treatment effect is tested under randomized, controlled and blinded conditions in those subjects who have met prespecified response targets. This has been recently advocated as an alternative design for analgesic clinical trials [13]. In this design scenario it should also be possible to mask (to both subject and assessor) the point at which the randomized switch occurs, but such a variation has not been adequately tested in long-term treatment trials.

## 7. Conclusion

In parallel randomization designs, we cannot rely on the placebo response to bottom out in a 4–5 week period. The evidence from placebo-controlled trials of >12-weeks duration using this design suggests that a placebo response continues beyond 12 weeks such that long-term trials run the risk of decreased separation of drug effect from placebo (assuming a maximum drug effect). The problem is magnified in trials in which a long titration period under blinded conditions is required and in which the analysis assigns trial dropouts as treatment failures. Efforts to enhance the observed treatment effect by suppressing the placebo response have generally not been successful and alternative trial designs need to be considered.

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