Systematic review: placebo response in drug trials of fibromyalgia syndrome and painful peripheral diabetic neuropathy; magnitude and patient-related predictors

Hauser W, Bartram-Wunn E, Bartram C, Reinecke H, Tolle T

CRD summary
The authors concluded that placebo cannot be recommended for management of chronic pain; a minimally important improvement in pain according to clinical benchmarks was found only in painful diabetic peripheral neuropathy trials. The authors’ conclusions reflect the evidence presented but lack of clarity in the analysis makes it difficult to confirm their reliability.

Authors' objectives
To determine the magnitude of placebo response on pain, to determine to what amount the placebo response accounts for the response in the active drug group and to test for potential characteristics of the patient and the patient-investigator interaction associated with the placebo response in patients with fibromyalgia syndrome and painful diabetic peripheral neuropathy.

Searching
MEDLINE, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL) and websites of the United States National Institutes of Health and the Pharmaceutical Research and Manufacturers of America were searched to July 2010. No language restrictions were applied. Reference lists of included articles and relevant reviews were handsearched.

Study selection
Double-blind randomised controlled trials (parallel or crossover designs) that compared any type of pharmacological medication with pharmacological placebos in patients with painful fibromyalgia syndrome and diabetic peripheral neuropathy were eligible for inclusion. The prespecified outcome measure was patient-rated pain intensity. The included studies were conducted in varied settings (America, Europe, Asia, mixed settings). Most of the included patients were women and Caucasians. Mean age was 47.6 years in fibromyalgia syndrome and 58.3 years in diabetic peripheral neuropathy trials. Types of active medications were varied and included antidepressants and anticonvulsants. The mean treatment durations were 10.6 weeks in fibromyalgia syndrome trials and 11.6 weeks in diabetic peripheral neuropathy trials. The mean pain score (range zero to 10) at baseline was 6.5 in fibromyalgia syndrome and 6.4 in diabetic peripheral neuropathy trials. All the fibromyalgia syndrome trials and most of the diabetic peripheral neuropathy trials assessed pain using visual analogue or numeric rating scales.

Two reviewers independently selected studies for inclusion; disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed independently by two authors using the Jadad scale. Key criteria assessed included randomisation, blinding and descriptions of withdrawals and drop-outs (scores ranged from zero to 5). Disagreements were resolved by discussion.

Data extraction
Two authors independently extracted outcome data using a structured form. Disagreements were resolved by discussion. Authors of primary studies were contacted in case of missing outcome data. Missing standard deviations were computed from t-values, confidence intervals or standard errors; values were imputed where calculations were not possible. All pain scales were converted to a zero to 100 scale.

Methods of synthesis
Pooled weighted mean difference (WMD) and standardised mean difference (SMD) and 95% confidence intervals (CIs) for change in pain scores (baseline to end of treatment) were calculated (separately for the treatment arms) using random-effects models. Statistical heterogeneity was assessed using the I² statistic. Meta-regression was used to assess
the impact of continuous potential predictors on pain outcomes. Subgroup and sensitivity analyses were conducted based on prespecified criteria. Publication bias was assessed using standard statistical tests.

**Results of the review**

Seventy-two trials that assessed fibromyalgia (mean number of participants 176) and 70 trials that assessed diabetic peripheral neuropathy (mean number of participants 200) were included in the review. The mean Jadad score for the fibromyalgia trials was 2.9 (standard deviation 1.8) and the mean score for the diabetic trials was 2.8 (standard deviation 1.7).

**Fibromyalgia syndrome:** Mean end of treatment pain scores were significantly higher than mean baseline pain scores in placebo groups (WMD 7.69, 95% CI 6.10 to 9.29; $I^2=71\%$) and in the fibromyalgia syndrome active drug group (WMD 17.11, 95% CI 16.41 to 17.90; $I^2=84\%$) on a pain scale of zero to 100.

Mean pain score was significantly higher in the active drug group (SMD 0.82, 95% CI 0.72 to 0.92; $I^2=77\%$) compared to fibromyalgia syndrome placebo groups (SMD 0.42, 95% CI 0.35 to 0.49; $I^2=53\%$).

**Painful diabetic neuropathy:** Mean end of treatment pain score was significantly higher than mean baseline pain score in painful diabetic neuropathy placebo groups (WMD 13.96, 95% CI 11.93 to 15.99; $I^2=85\%$) and in active drug groups (WMD 22.54, 95% CI 20.49 to 24.58; $I^2=85\%$) on a zero to 100 pain scale.

Mean pain score in the active drug group (SMD 1.14, 95% CI 1.02 to 1.25; $I^2=85\%$) was significantly higher than mean pain score in the painful diabetic peripheral neuropathy placebo groups (SMD 0.71, 95% CI 0.61 to 0.81; $I^2=81\%$).

No evidence of publication bias was found. Subgroup and sensitivity analyses yielded no significant results.

**Meta-regression:** Factors associated with pooled weighted mean difference of placebo on pain in both fibromyalgia syndrome and painful diabetic neuropathy trials were pain baseline, incremental year of study initiation and effect of active medication on pain. Pooled estimates of effects differed by number of study sites for fibromyalgia syndrome trials only.

**Authors’ conclusions**

A minimally important improvement in pain according to clinical benchmarks was only found in painful diabetic peripheral neuropathy trials; placebo cannot be recommended for the management of chronic pain.

**CRD commentary**

The review inclusion and exclusion criteria were clearly stated. Several electronic databases (except EMBASE) and grey literature sources were searched without any language restrictions. Review processes were done in duplicate and this minimised potential error and bias. Study quality was assessed using the Jadad summary score approach and this makes it difficult to see how the trials were scored and omitted some important criteria. Random-effects meta-analysis was used. There was no clear explanation or exploration for the large observed between-study variations.

The authors’ conclusions reflect the evidence presented but the lack of clarity in the analysis makes it difficult to confirm their reliability.

**Implications of the review for practice and research**

**Practice:** The authors stated that contextual factors (such as positive expectations and suggestions) should be used in clinical practice to empower the effects of active drug therapy.

**Research:** The authors did not state any implications for research.

**Funding**

Not stated.

**Bibliographic details**

2011; 152(8): 1709-1717

**PubMedID**
21429668

**DOI**
10.1016/j.pain.2011.01.050

**Original Paper URL**
http://www.painjournalonline.com/article/S0304-3959(11)00088-1/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Analgesia /methods; Databases, Factual /statistics & numerical data; Diabetic Neuropathies /drug therapy; Fibromyalgia /drug therapy; Humans; Meta-Analysis as Topic; Placebo Effect; Randomized Controlled Trials as Topic; Reproducibility of Results; Treatment Outcome

**AccessionNumber**
12011004929

**Date bibliographic record published**
09/11/2011

**Date abstract record published**
09/01/2013

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.