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Critical Reviews

Placebo Responses in Long-Standing Complex Regional Pain Syndrome: A Systematic Review and Meta-Analysis

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Abstract: **The typical placebo response (ie, the nonspecific effects in the placebo group including benign natural course, regression to the mean, expectation/conditioning effects, and others) in randomized trials in complex regional pain syndrome (CRPS) is unknown. We recently observed a surprising near-absence of placebo response in a randomized controlled trial we conducted on patients with long-standing (≥6 months) CRPS. To investigate the idea that there may be an absence of placebo response in long-standing CRPS further, we conducted a systematic review and meta-analysis of placebo responses in randomized controlled trials conducted in patients with CRPS of ≥6 months. We systematically identified suitable randomized controlled trials published between 1966 and September 2013. We calculated the mean difference and standard error of the mean difference for placebo responses and synthesized individual effect sizes at 4 specified time periods of interest (15–30 minutes, 1 week, 3–4 weeks, and 6 weeks or more) via meta-analysis using the method of inverse-variance. Heterogeneity was assessed according to the I^2 statistic. For primary analysis, we pooled trial-specific effect sizes over the 4 time points. We analyzed data from 340 participants from 18 trials out of a possible 361 participants from 20 trials (94% of participants analyzed). Significant heterogeneity was present between trials; therefore, we interpreted trends from visual inspection of individual trials and pooled estimates. Placebo response was significant at the earliest time period (15–30 minutes). There was no significant evidence of placebo response at any of the other time periods. These results inform the design of future trials, and they caution against the "therapeutic" use of placebo in long-standing CRPS.**

Perspective: ***In this meta-analysis of placebo responses in randomized controlled trials in long-standing CRPS, published during 1966 to 2013, we found no evidence for placebo analgesia, except at very early time points. Results inform the design of future placebo analgesia research in long-standing CRPS.***

Key words: *Complex regional pain syndrome, reflex sympathetic dystrophy, placebo response, randomized controlled trials, meta-analysis.*

The term *placebo response* or *placebo effect* in clinical trials usually describes the combination of all effects that are not specific to the active trial intervention. In analgesia trials, the placebo response is the sum of pain relief due to a pain condition's benign natural course, pain regression to the mean,[65] and a "true

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placebo mechanism." The latter is of context-related magnitude[32,64] and caused by mixed factors, including expectation and conditioning.[16] Since Beecher's pivotal studies in the 1950s, placebo responses in pain conditions have generally been seen as particularly large.[2,3,60] However, these studies were based predominantly on the review of results from acute pain trials, and often the definition of a placebo response was based on the percentage of patients who had any pain relief with placebo, rather than on the percentage of pain relief in the placebo-treated group.[2,3,60] More recent investigations on placebo responses in *chronic* pain trials have suggested that specific chronic pain conditions have specific expected placebo responses that are generally much smaller than those reported in the earlier trials.[15,28,32,36,52] Understanding the sizes of condition-specific placebo responses is important because such information can influence the choice of condition for new compound testing and the design of clinical trials, where, for example, smaller sample sizes will be required when conducting power calculations if smaller placebo responses are expected.[36] Understanding the size of placebo response also helps determine whether a placebo could be used to achieve therapeutic effects.[35] Finally, placebo response sizes may also convey information about disease-associated neurobiological processes.[16]

Complex regional pain syndrome (CRPS) is a severe chronic pain, predominately affecting distal limbs after trauma.[21,42] Most patients with CRPS improve within the first few months after disease onset, so their response to placebo in a clinical trial would be expected to be large because of the benign natural disease course.[11] We recently observed a surprising near-absence of placebo response in our randomized controlled trial (RCT) in patients with CRPS of more than 6 months' duration.[23] Other authors have made similar observations in their trials,[44,56] with, for example, Munts et al[44] reporting an overall placebo response of 0% in their trial. We wondered whether it might be the case that long-standing CRPS does not demonstrate placebo response, and therefore we have conducted a systematic review and meta-analysis of placebo responses across RCTs in patients with long-standing (≥6 months) CRPS. To our knowledge, this is the first review of placebo response in CRPS.

Methods

Systematic Search Strategy and Selection of Trials

RCTs for the treatment of CRPS were identified from the reference lists of trials from 2 systematic reviews of treatments for CRPS. A review by Forouzanfar et al[19] identified 28 RCTs published from 1966 to June 2000, and a subsequent review by our group[10] identified 43 RCTs from July 2000 to February 2012 using similar methodology; see Supplementary Appendix A for the detailed search methodology for both reviews. We also repeated the search outlined in Cossins et al[10] for the time period from March 2012 to September 2013, searched the reference lists of included trials, and searched trial registries for any details of ongoing trials or unpublished work. Two authors (G.K.M. and S.J.N.) independently screened all eligible trials according to the inclusion criteria below. Any disagreements were resolved by mutual discussion or through adjudication via the senior author (A.G.).

Inclusion Criteria

- RCTs for the treatment of CRPS type I or II in adults
  - We included trials in which a diagnosis CRPS was made using the original International Association for the Study of Pain (IASP) criteria,[3] the more recent Budapest criteria (ie, the "new IASP criteria"),[27] or criteria for the diagnosis of reflex sympathetic dystrophy.[17]
  - Trials in the reviews[10,19] conducted in mixed populations of CRPS and non-CRPS patients were included if results were available for CRPS patients as a subgroup.
  - Trials of all sample sizes were included; we did not specify a minimum sample size for inclusion.
- Single-blinded (participants) or double-blinded (participants and investigators) trials
  - Inadequate blinding of trials may introduce performance and/or detection bias into results; therefore, we made a judgment on the adequacy of blinding in each of the trials (high, low, or unclear risk of bias of blinding; see Supplementary Appendix B for details).
- Trials of a parallel or crossover design
  - In trials of a crossover design, we made a judgment on the presence of a possible carryover effect (see Supplementary Appendix B for details). If for any such trial we considered a carryover effect to be present, we included only data from the group that received placebo treatment first. If data were not reported by treatment period, we excluded the trial.
- Trials with at least 1 active treatment arm and a placebo arm
  - We recorded the route of intervention of active and placebo treatment (intravenous [i.v.], oral, percutaneous, etc) and made a judgment on invasiveness of the intervention (high, medium, or low level of invasiveness; see Supplementary Appendix B for details).
  - We scrutinized all placebo treatments for the possibility of either active or nocebo (negative or harmful) effects.
- Trials that reported an outcome of participant-reported pain intensity on the visual analog scale (VAS) or numeric rating scale (NRS) before and after intervention, or change in pain intensity score from baseline by treatment arm
  - We excluded trials for which we were unable to obtain pain intensity scores in the placebo arm.