
TITLE: DO ENVIRONMENTAL PARAMETERS INFLUENCE THE PREDICTION OF THE PLACEBO RESPONSE?

Abstract

This proof-of-concept study on peripheral neuropathic pain patients investigates the potential influence of the investigator on the placebo response in RCTs while manipulating different variables, including patient expectation, conditioning and prior experiences, observational and social learning.

PNP patients were given a blinded placebo (presented as “new treatment”) in addition to their regular analgesic treatment. They were randomized to follow a “Influenced” or sham procedures designed to assess the environmental factors that may influence the placebo response when administering a drug.

41 completed the study. They suffered from PNP based upon medical examination for at least 6 months. The sex ratio was 21:22 (49/51%) for males and females, respectively. The mean age of the patients was 57 years old (SD=11.4). The median history of PNP was 7.2 years.

The 20 patients in the “Influenced” group followed the studied placebo-reinforcing procedure consisting of positive expectation directed information about the placebo in the form of a video. The patient then underwent pre-treatment heat pain stimuli. After the pain stimuli, patients were given their first placebo capsule and underwent a new heat pain conditioning approximately one hour after dosing. The post-treatment heat pain conditioning protocol was intentionally modified from the pre-treatment, one as the mean intensity was reduced to induce the patient’s belief in analgesic efficacy.

The 21 patients randomized to the “Sham” group followed the Sham procedure consisting of no expectation of improvement, neutral social observational learning and no modulation of pain stimuli. Those patients watched a video presenting only neutral properties of T4P1001 drug (placebo). Both groups were given capsules to be taken twice a day over 4 weeks as add-on therapy to their regular analgesic.

The weekly mean of the average pain score (APS; computed on a 11-point numerical rating scale) at baseline was 5.3. After four weeks of placebo treatment, across groups, 12 patients (30%) had an important decrease of their average pain of more than a 20% from baseline. Overall, the mean APS decreased significantly by 0.7 (effect size=-0.50; p-value=0.0047) to 4.6. The 20 patients in the “Influenced” group had a significant decrease by 0.9 (95%CI=[0.2,1.6]; p-value=0.0167) of their mean APS. The decrease was less important in the sham group with a decrease by 0.5 (95%CI=[-0.2,1.1]; p-value=0.12785). However, the difference of decrease between the two procedures was not significant (p-value=0.4162).

The global magnitude of the mean placebo effect was considered as moderate but in accordance with published meta-analysis in chronic pain. This relatively mild placebo response could be explained by the mode of administration. The placebo given as an add-on therapy may have decreased the expectation associated to efficacy of the treatment. Yet, one third of the patients demonstrated a strong placebo response.

If the patients following the “Influenced” procedure seemed to have a more important decrease of APS, they were not significantly different from the “Sham” group. This marginal difference 0.9 vs 0.5

(respectively for influenced and sham group) should be put into perspective with individual variation. Indeed, both groups had a wide range of placebo responses and a high variance. The “Influenced” group responses ranged between -2.0 and 4.4 (sd=1.49). The “Sham” patients were comprised between -1.1 and 5.4 (sd=1.43). This high individual variation combined with small sample sizes could explain better the likelihood of an observed center effects than a true investigator bias.

To control the increasing placebo response affecting the assay sensitivity in RCTs, many study level factors have been studied such as number and type of patients, study design and outcome measurement. An other aspect investigated here on peripheral neuropathic pain patients is the potential influence of clinical investigator sites on the placebo response. We tried to mimic and maximize it while manipulating the patient expectation and conditioning through two different procedures. Our results, however, show that the “true” site effect is marginal compared to the intrinsic placebo fluctuations. This advocates for a better characterization of the individual placebo response. The prediction of the placebo responders may be used in RCTs to stratify patients within groups, and thereby to increase the assay sensitivity.

Authors

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