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TITLE: **MULTIFACTORIAL ASPECT OF THE PLACEBO ANALGESIA RESPONSE IN PERIPHERAL NEUROPATHIC PATIENTS**

Abstract

The placebo response exerts a confusing influence when testing the statistically significant superiority of active compounds compared to placebo in analgesia randomized clinical trials (RCTs). Furthermore, the magnitude of this effect has tended to increase over time with the year of trial completion, including in neuropathic pain trials. The main objective in this proof-of-concept study was to investigate parameters that influenced the placebo response in PNP patients. In particular, we investigated psychological predictors of the placebo response which had until now mainly be studied in healthy volunteers. Observed patient's characteristics included personality traits from validated scales as well as medical / disease history and pain characteristics.

To investigate the analgesic effect of a placebo, forty-one patients with peripheral neuropathic pain (PNP) were given a blinded placebo in addition to their regular analgesic treatment during four weeks. However, patients were under the impression of receiving a new treatment therapy. The placebo response was captured with the improvement of the weekly mean of the average pain score (APS; computed on a 11-point numerical rating scale) after the placebo administration. Patients with more than 20% reduction of pain intensity were considered as placebo responders. T-tests were used to compare placebo responders and non-responders and to identify possible predictors.

After four weeks of placebo treatment, the mean APS decreased significantly by 0.7 (effect size=-0.50; p-value=0.0047) from a 5.3 baseline APS. The magnitude of the effect was considered as moderate but in accordance with meta-analysis in chronic pain (Hróbjartsson and Gøtzsche 2006). This relatively mild placebo response could, however, 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 (Finniss et al. 2010). However, twelve patients (30%) were considered as "placebo responders". Those patients had an average of 48% reduction of pain intensity.

Eleven features were different between the placebo responders and non-responders. Six features (55%) were personality traits showing the interest of such psychological predictors for the individual characterization of the placebo response. Those features were related to the expectations, the agreeableness and the extraversion. Such personality traits were already highlighted in the literature to be linked with the placebo effect. In particular, the expectation features were positively correlated with the responders. In the medical history, two features (18%) were related to the number of drug taken by the patients. Patients with more treatments had a lower response in our study. To the best of our knowledge this was never described before in the literature. The other features were linked to the disease intensity (2 features, 18%) and the demographic (1 feature).

This proof-of-concept study on PNP patients shows the importance of the psychological traits on the individual characterization of patient placebo response. Those results confirm also its multifactorial aspect. The prediction of the placebo response should be based on a combination of features from the demographics, the disease intensity and the medical history as well as personality traits. These results make a step toward the characterization and the prediction of the placebo response, a major confounding factor, in RTCs

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