Modeling of Peripheral Neuropathic Pain and Osteoarthritis placebo response: working towards a unique model of the placebo response in chronic pain?

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Introduction and Motivation

In analgesia randomized clinical trials (RCTs), the magnitude and the variability of the placebo response negatively impacts the ability to demonstrate superiority of active compounds compared to placebo.

The main objective of this analysis was to investigate predictivity of the placebo response in Peripheral Neuropathic Pain (PNP) and Osteoarthritis (OA) as a way to control for this major confounding factor.

This is part of a larger effort to evaluate the feasibility of building a model of the placebo response generalizable to several chronic pain diseases.

Study Designs and Patients

Peripheral Neuropathic Pain (PNP):

- 2 studies
  (ECT 2013-005445-16 and 2015-001034-25)
- 87 patients;
- 4 weeks of blinded placebo treatment b.i.d. as add-on therapy.

Osteoarthritis (OA):

- 2 studies
  (ECT 2015-001034-25 and 2017-001028-23)
- 48 patients;
- 1 or 3 months of blinded placebo treatment b.i.d. as add-on therapy.

All patients were recruited from site database.

Patient data

Baseline data:

- Psychological questionnaire assessing their personality;
- Weekly mean of daily average pain score (APS);
- Brief pain inventory (BPI);
- Investigator and Patient global assessment of change (IGAC and PGAC);
- Demographics and medical history.

For all studies, the primary endpoint was reduction in the weekly mean of daily average pain score (APS).

Placebo response :
The placebo response was defined as the change from baseline (last 7 days before the first dose) to end-of-treatment (last 7 days before the end-of-treatment) of the APS.

Modeling the placebo response

Modeling:
The placebo response was modeled as linear combination of the baseline patient's data learned with a Support Vector Regression (SVR).

Baseline features selection:
The baseline features used in the model were selected using a Repeated Feature Elimination procedure (RFE).

Performance Evaluation:
The models were tested in Monte Carlo cross-validation. Repeatedly, the patients were split between 90% of patients used for the training and 10% for testing.

The performance of the models were computed in terms of correlation and R-squared between the actual and predicted placebo responses on the validation sets. The average performance on all validation sets is reported.

Results

For the analyses, two populations of patients were defined:

- PNP : the PNP patients only (N = 87);
- PNP + OA : the pooled populations of PNP and OA (N = 135).

PNP Model:
The PNP population was used to learn and to evaluate the performance on PNP or PNP + OA population. The model learned on the PNP population was able to predict the placebo response of patients from both PNP and PNP + OA populations.

Table 1: Perfomances of the PNP model.

Population	N	#Feat*	Correlation	95% CI	P-value	R-squared
PNP	87	12	53.7%	[36.8 , 67.2]	<0.001	28.9%
PNP + OA	135	12	49.3%	[35.4 , 61.1]	<0.001	24.3%

PNP+OA Model:
The PNP + OA population was used to learn and to evaluate the performance on PNP or PNP + OA population. The model learned on both PNP and OA patients had similar performance to the PNP models.

Table 2: Perfomances of the PNP + OA model.

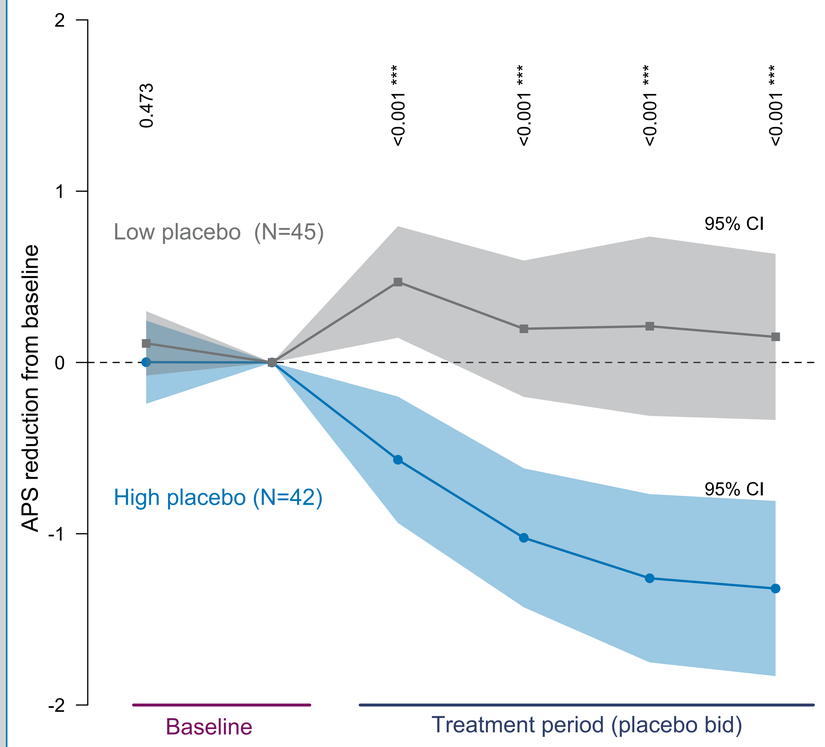
Population	N	#Feat*	Correlation	95% CI	P-value	R-squared
PNP	87	12	53.9%	[37.1 , 67.4]	<0.001	29.1%
PNP + OA	135	12	53.5%	[40.2 , 64.5]	<0.001	28.6%

* #Feat : is the number of baseline features included in the model.

Model prediction

The PNP + OA model was used to split the PNP patients between High and Low placebo responders.

- Low Placebo: Below average predicted placebo response.
- High Placebo: Above average predicted placebo response.



Conclusion

These results demonstrate the similarity in the factors predictive of the placebo response in both PNP and OA patients.

In particular, a model built on PNP patients was able to predict the placebo response of both PNP and OA patients.

As a covariate, the model predictions could be used to reduce the impact of the placebo response-related variance in analgesia clinical trials. This reduction of variance could lead to increased effect size and study power.