On the relationship between pain variability and relief in randomized clinical trials

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1. Background

- To ensure a statistically significant drug effect, clinicians and pain researchers look to exclude high "placebo responders" before the intervention phase of randomized clinical trials.
- Higher placebo response (or greater relief in the placebo group) in patients enrolled in randomized clinical trials is associated with higher baseline pain variability.
- Previous research on this relationship does not account for confounding variables (pre-intervention pain and natural history of disease).

2. Research Objectives

Derive the strength of the relationship between baseline pain variability and relief while controlling for the effects of pre-intervention pain and natural history between treatment groups.

3. Methods

- Longitudinal pain data were obtained from two clinical trials (Placebo I and Placebo II):
  - Placebo I:
    - 18 Controls: 46 years ± 14
    - 43 Placebo-treated patients: 46 years ± 13
  - Placebo II:
    - 11 Controls: 57 years ± 12
    - 32 Placebo-treated patients: 57 years ± 9
    - 30 Drug-treated patients: 52 years ± 14
- Used multiple regression model with linear contrasts to isolate treatment effects:
  - **post ~ pre + group*sd**
    - **post**: post-intervention score
    - **pre**: pre-intervention score
    - **group**: treatment group
    - **sd**: baseline pain variability
- Obtained semi-partial correlations between baseline pain variability and relief from multiple regression model

4. Results

		r_{sp} (CI)
Placebo I	No treatment (n = 18)	−0.16 (−0.39, 0.08)
	Placebo (n=43)	0.13 (−0.08, 0.37)
Placebo II	No treatment (n=11)	0.08 (−0.11, 0.31)
	Placebo (n=32)	0.01 (−0.15, 0.20)
	Drug (n=30)	−0.11 (−0.26, 0.06)

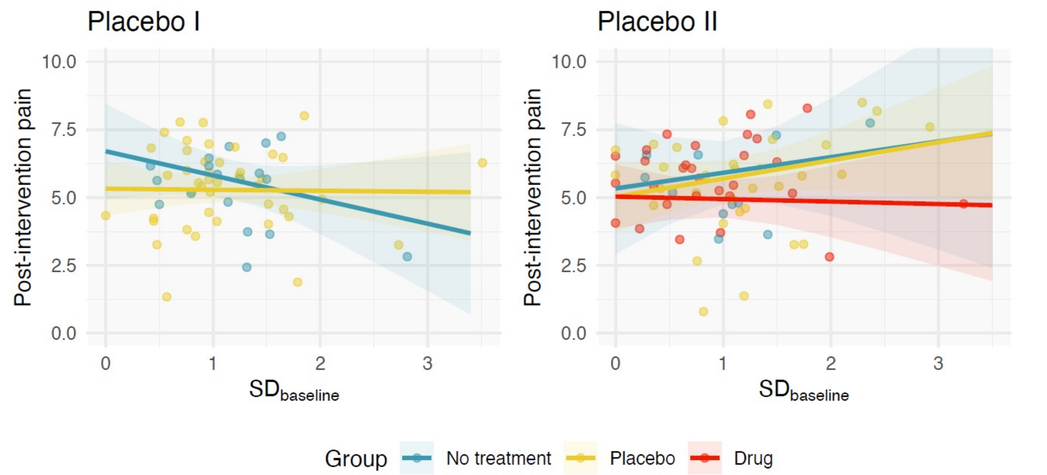

Figure 1. Adjusted post-intervention pain as a function of $SD_{baseline}$ and group.
We fit a linear regression to each study, which modeled post-intervention pain as a function of pre-intervention pain, $SD_{baseline}$, and group. Here, we depict the adjusted relationship between $SD_{baseline}$ and post-intervention pain (on the right) after adjusting for pre-intervention pain. In Placebo I, the "no treatment" group has a weak negative correlation; however, this is driven by a single data point (see Figure 2); the "placebo" group's $SD_{baseline}$ is not correlated with post-intervention pain. In Placebo II, the "no treatment" and "placebo" groups show a weak, positive relationship whereas the "drug" group exhibits approximately no relationship. The raw, semi-partial correlations are included on the left.

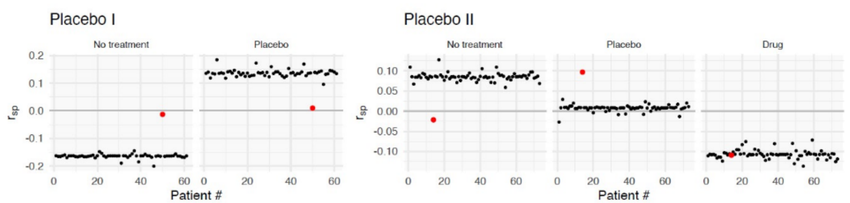

Figure 2. Influence of individual patients on the semi-partial correlations.
Each point represents the semi-partial correlation when patient *x* is removed from the analysis. This leave-one-out analysis reveals that in both Placebo I and Placebo II, there was one participant who strongly drove the results (red points). Removing the individual in Placebo I tends to produce semi-partial correlation coefficients that are much closer to zero for both groups. Removing the individual in Placebo II to decrease the no treatment semi-partial correlation and increase the placebo semi-partial correlation. In both cases, our conclusions are unaffected since appreciable, negative semi-partial correlations do not appear in the placebo groups.

5. Conclusions

- The relationship between pain variability and relief is weak and inconsistent.
- Pain variability should not be used as a univariate predictor of relief in any group of a clinical trial; may hold *some* value as a covariate to improve statistical efficiency if it is able to capture variance.
- Multivariable approached can be generalized to other analyses, and may provide unique information relative to standard univariable analyses.

6. Acknowledgements

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