

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

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Background

- Placebo response in clinical trials - “improvement in pain due to the psychological effect of receiving treatment”
- Drug effect is measured in clinical trials; $\text{Drug effect} = \text{Drug relief} - \text{Placebo relief}$
- High placebo response leads to “clinical trial failure” or a small drug effect
 - EXAMPLE:
 - Drug relief: -5,
 - Placebo relief: -1 vs. -3
 - Drug effect: -4 and -2

Background (cont.)

- Current research aims to find correlates that predict placebo responders
- Pain variability: previously identified correlate of placebo response
- Previous research does not account for confounding variables (pre-intervention pain and natural history of disease)

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**.

Methods

- Used data from two clinical trials; both included no treatment (no_tx) and placebo groups, only one included a drug group (Placebo II)
- **post** ~ **pre** + **group*****sd** (**group** is a factor, used for linear contrasts)
 - included pre-intervention pain as a covariate to control for pre-intervention pain
 - isolated effect by group to control for natural history by using linear contrasts
 - placebo improvement = no_tx + placebo
 - drug improvement = no_tx + placebo + drug
 - drug = drug improvement - placebo improvement = (no_tx + placebo + drug) - (no_tx + placebo) = drug

Methods (cont.)

- Calculated semipartial correlations using multiple regression model (**post** ~ **pre + group*sd**)
 - variance accounted for by ONE variable; reduces confounding effects

$$r_{sp} = \text{sgn}(t) \sqrt{\frac{t^2(1 - R^2)}{df}}$$

r_{sp} = semipartial r

t = t -statistic (of variability)

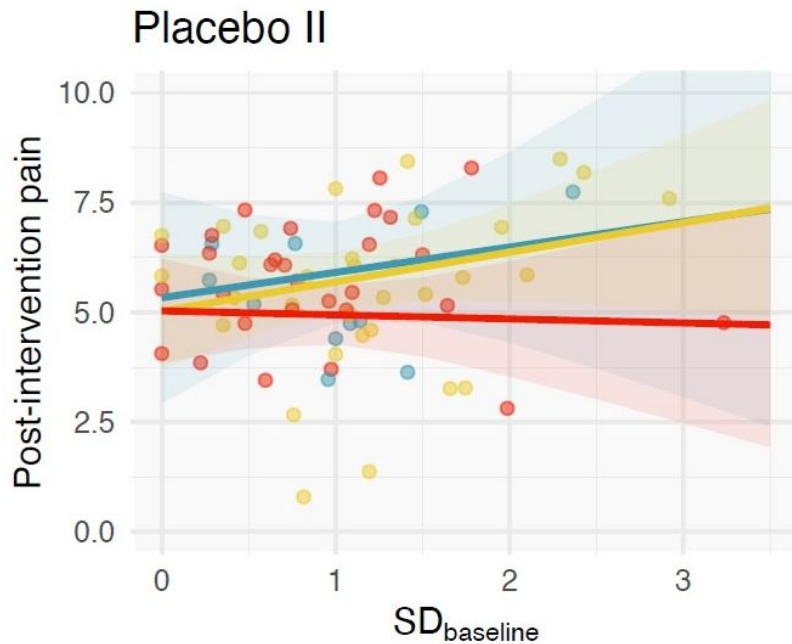
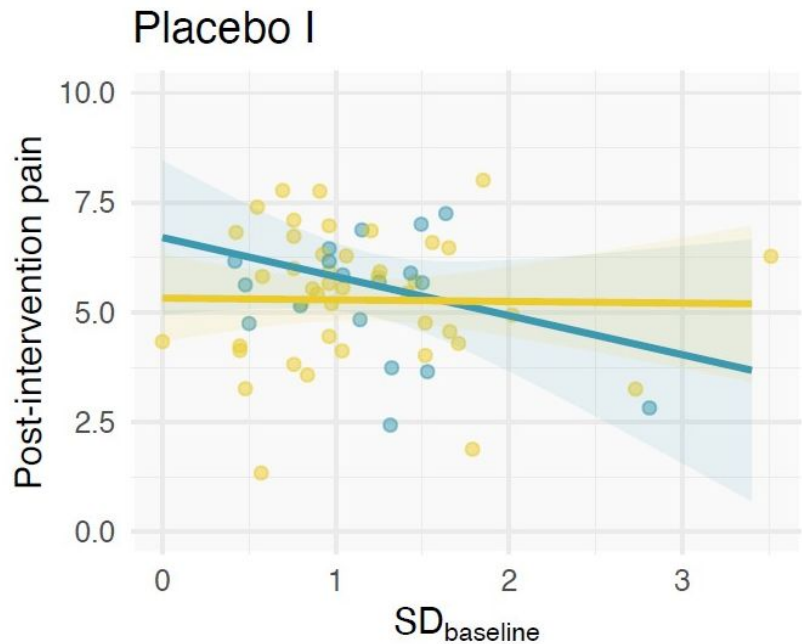
R^2 = model coefficient of determination (global fit of the model)

df = residual degrees of freedom

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)

Results (cont.)



Group No treatment Placebo Drug

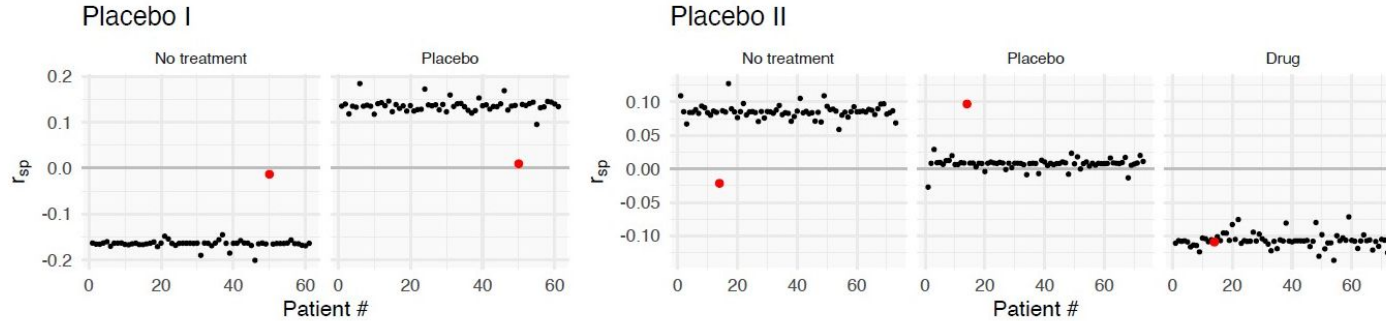
Conclusions

The relationship between pain variability and relief is weak and inconsistent; should not be used as a univariate predictor of relief in any group of a clinical trial

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Sensitivity Analysis



Supplementary Figure 1. 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.

Correlations without “the model”

			r_{sp} (CI)
Within-group change score, no pre covariate	Placebo I	No treatment (n = 18)	-0.33 (-0.73, 0.23)
		Placebo (n=43)	0.16 (-0.23, 0.45)
	Placebo II	No treatment (n=11)	0.31 (-0.80, 0.79)
		Placebo (n=32)	0.28 (-0.09, 0.52)
		Drug (n=30)	0 (-0.27, 0.40)
Within-group, with pre covariate	Placebo I	No treatment (n = 18)	-0.30 (-0.61, 0.19)
		Placebo (n=43)	0 (-0.37, 0.28)
	Placebo II	No treatment (n=11)	0.68 (-0.20, 0.91)
		Placebo (n=32)	0.22 (-0.16, 0.52)
		Drug (n=30)	-0.10 (-0.40, 0.42)