ON THE RELATIONSHIP BETWEEN PAIN VARIABILITY AND RELIEF IN RANDOMIZED CLINICAL TRIALS

Siddharth Tiwari**,** with Andrew Vigotsky and A. Vania Apkarian

PREFACE

Pain is tricky to study. Along with being the most prevalent chronic medical condition in the world, pain forces us to combine our understanding of physiology and the philosophy of the self and mind. This is because pain is considered a "subjective experience", limited to the individual themselves.

We can think of many examples where two different people are presented with the same stimuli or situation and produce a different response: stubbing a toe or holding a hot object, for example. There are even situations where we may respond to stimuli that shouldn't result in pain. A famous example from 1995 describes a 29-year-old builder who jumped onto a 7-inch nail. He wailed in pain on his stretcher and the ambulance as the nail stuck out of both sides of his steel-toed boot. But when the doctors peeled off the builder's boot, they found that the nail hadn't penetrated any part of his foot. It had passed between his toes, without a scratch.

This is the problem of chronic pain. Normal, or acute pain, presents itself within individuals when one encounters painful stimuli; researchers believe that this is possibly part of an evolutionary mechanism within humans to protect themselves from life-threatening situations. This means we constantly assess our surroundings for potentially harmful stimuli, and when we feel pain, it's because our brain senses a potential problem. In contrast, chronic pain persists without a stimulus, becoming increasingly painful as it develops. This means pain is entirely psychological or subjective. At this moment, no medication can cure a person of chronic pain. Opioids are the only medications capable of analgesia (reducing pain) effectively and consistently enough for chronic pain, which carry the potential risk of addiction and overdose.

Several members of my family in India suffer with chronic pain in various forms, which they attempt to fight with over-the-counter medicine and homemade herbal remedies. Some of them refuse to take their prescribed opioids because of the risk of addiction.

While visiting India, I'd sometimes be tasked to bring them their Tylenol or *chai* if their pain flared up. They'd also frequently ask each other how much pain they're in on a scale of one to ten; they'd hold up their fingers promptly on one or two hands.

It fascinated me. Even though an aunt suffered with fleeting lower back pain and a great-uncle suffered with a slow burn on his knees, they could both hold up six fingers: their pain was entirely different, yet they both held five fingers on one hand and one finger on the other. My paternal grandma's knee pain would randomly come back at nine fingers after being only one or two for the past three days whereas my uncle's pain would always stay between five and seven fingers without budging.

For this reason, as I grew older, I became interested with quantifying and modeling chronic pain's longitudinal trajectory (development/change over time). The confusion that I'd felt when seeing my family members report their pain were among the exact problems that

chronic pain researchers grapple with; we simply do not understand or have the ability to precisely predict how pain changes and develops within subjects. By focusing efforts to understand pain's development within and between subjects, we could help clinicians offer treatment more specific to subjects as well as help clinical trials identify possible, non-opioid pain medications with more efficiency. It would also offer more insight into scientifically interpreting other types of qualia or subjective experience, which could fill gaps in our understanding of thought, perception, and behavior.

To learn more about this area, I immersed myself in statistics, particularly linear regression and Bayesian statistics. Thankfully my research mentors, Andrew Vigotsky and Dr. A.V. Apkarian, always welcomed my frequent questions and confusion. Through months of their guidance and opportunities to research, I began to see math's ability to simplify even the most complex of phenomena. It felt like art: with different types of regression, you'd canvas hundreds of thousands of data points onto a 600 x 600-pixel canvas. You'd know when you'd have made a masterpiece, because the points would align in a way where everything would make sense.

There are potential pitfalls for these paintings of the world, unfortunately. A simple linear regression, used improperly, can be overwrought with bias and confounding effects. With the increased availability of data available to the public, it has become increasingly dangerous to make assumptions of the world around us. It is the premise of the project that I present to you today. My project challenges almost two decades of research that confirms the presence of a statistical phenomena and practice within analgesic clinical trials that could have potentially invalidated their results.

Pain or not, to produce a more accurate, working model of the world, it is necessary that the data that we obtain, the methods that we use to analyze them, and the conclusions that we draw, operate on valid assumptions and understanding. This is the power of combining mathematics and science; we're able to unearth previously invisible relationships around us. There is so much left to operationalize, to reason, to understand. With this in mind, don't forget to challenge your own assumptions as well as the assumptions of the world around you to bring forth a clearer understanding of the tricky things in our world. This is where the progress of science lies.

INTRODUCTION

Randomized clinical trials are the principal method by which researchers assess treatment efficacy. Although clinical trials can provide valid evidence of a treatment's average effect (relative to some control), they often fail to demonstrate meaningful drug effects relative to placebo. Some researchers have cited high "placebo response" as the main cause of these "failures" (Khan et al., 2003; Katz et al., 2008; Tuttle et al., 2015; Alexander et al., 2021), suggesting it may be prudent to exclude "high placebo responders" prior to trial commencement.

Researchers have sought out correlates to predict pain relief in the placebo-treated group, which could then be used to exclude patients who would contribute to clinical trial "failure" via their "placebo response." One of these identified correlates is pain variability, which has been shown to negatively correlate with subsequent pain relief in the placebo-treated group across several chronic pain conditions (Harris et al., 2005; Farrar et al., 2014; Treister et al., 2019). In other words, patients with the greatest pain variability at baseline tend to have the greatest decreases in pain following placebo administration. This relationship is specific to pain relief in the placebo group in some (Farrar et al., 2014) but not all studies (Treister et al., 2019), and even absent in others (Gillving et al., 2022).

Although previous work demonstrates a relationship between baseline pain variability and pain relief, other factors such as regression to the mean and natural history can contribute to improvements in pain reports (Dworkin et al., 2012; Farrar et al., 2014). Indeed, previous studies have acknowledged, but have not accounted for, the influence of these factors on decreases in pain reports. In this work, we aim to improve our understanding of the prognostic value of baseline pain variability by adjusting for baseline pain, natural history, and regression to the mean. Since baseline variability is simple to collect and calculate (cf. neuroimaging and genetic traits that are also correlated with greater pain relief following placebo; e.g., (Hall et al., 2012; Vachon-Presseau et al., 2018)), its prognostic value and (placebo-) specificity could be easily exploited in both trials and practice.

METHODS

Datasets

This was a secondary analysis of two, previously published randomized, double-blind, placebo-controlled trials conducted by our research group at Northwestern University in Chicago, IL. **Table 1** contains the demographic characteristics of each study's subjects.

Table 1: Demographic Characteristics of Placebo I and Placebo II.

		Age (SD), years	**Women (%)**
Placebo I	No treatment (n = 20)	46 (13)	10 (50)
	Placebo (n=43)	46 (12)	14 (33)
	All (n=63)	46 (12)	24 (38)
Placebo II	No treatment (n=11)	55 (10)	7 (64)

	Placebo (n=32)	58 (10)	18 (56)
	Drug (n=33)	53 (14)	12 (36)
	All (n=76)	55 (11)	38 (52)

Statistical Analysis

All analyses were performed using R (R Core Development Team, 2020). We built a single linear regression model for each study (2 in total), using pre-intervention pain (mean of the first 7 days in the pre-intervention period), group, and baseline pain variability ($SD_{baseline}$, calculated as the standard deviation of the pre-intervention phase) as independent variables and post-intervention pain (mean of the last 7 days in the intervention period) as the dependent variable. In addition to these three independent variables, we included the interaction between group and $SD_{baseline}$ (herein referred to as group×$SD_{baseline}$ interaction) to isolate the effect of $SD_{baseline}$ on post-intervention pain by group. The effects of group and the group×$SD_{baseline}$ interaction were computed using modified backward contrasts, in which each group was compared to the previous group (placebo I: placebo vs. no treatment; placebo II: placebo vs. no treatment, drug vs. placebo) and no treatment was the intercept or reference group. This was done to compare the additive effect of placebo relative to no treatment and drug relative to placebo, meaning that the previous level controls the level succeeding it, thereby adjusting for natural history (since the no treatment group represents the natural course of pain), regression to the mean (through the pre-intervention score covariate and no treatment group), and placebo effects. Specifically, the following contrast matrices were used to compare differences between the two groups:

$$\mathbf{C}_{\text{Placebo I}} = \begin{bmatrix} \mathbf{1} & \mathbf{0} \\ \mathbf{1} & \mathbf{1} \end{bmatrix},$$

$$\mathbf{C}_{\text{Placebo II}} = \begin{bmatrix} \mathbf{1} & \mathbf{0} & \mathbf{0} \\ \mathbf{1} & \mathbf{1} & \mathbf{0} \\ \mathbf{1} & \mathbf{1} & \mathbf{1} \end{bmatrix}.$$

The rows of these matrices denote the groups in each study (factors for no treatment in row 1, placebo in row 2, and drug in row 3) and the columns represent the weight of each parameter on that group. This is mathematically equivalent to dummy coding such that patients in the no treatment group receive a 0 for placebo and 0 for drug; patients in the placebo group receive a 1 for placebo and 0 for drug; and patients in the drug group receive a 1 for placebo and 1 for drug. These contrasts enabled us to isolate the effects of $SD_{baseline}$ on post-intervention pain by group.

After obtaining the isolated effects, we calculated semi-partial correlations ($r_{sp} = \text{sgn}(t)\sqrt{\frac{t^2(1-R^2)}{df}}$, where t is the t-statistic of the effect of interest, R^2 is the model coefficient of determination, and df is the residual degrees of freedom) between $SD_{baseline}$ and post by group. Compatibility intervals (CI) for r_{sp} were calculated using the bias-corrected and accelerated bootstrap with 1,000 replicates. Data are depicted using adjusted effects (DuMouchel, 1988).

RESULTS

In total, 139 subjects were examined (63 subjects in Placebo I; 76 subjects in Placebo II). **Figure 1** depicts the independent relationship between baseline pain variability and relief for each group after adjusting for pre-intervention pain, allowing each group to have a different effect of baseline pain variability. Model parameters and semi-partial correlations associated with adjusted group effects can be found in **Table 2**. Including $SD_{baseline}$ in the models as a linear (not interactive) predictor increased Placebo I and Placebo II model R^2's by 0.01.

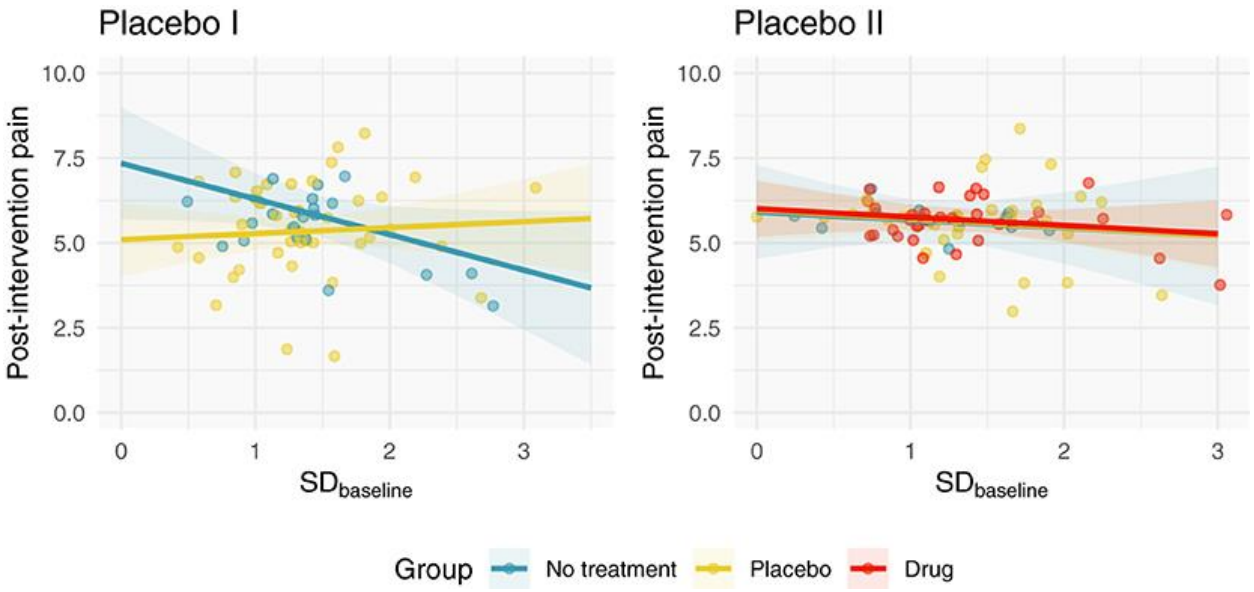

Figure 1. ***Adjusted post-intervention pain as a function of $SD_{baseline}$ and group.***
We fit a linear regression to each study, which modeled post-intervention pain as a function of pre-intervention pain, $SD_{baseline}$, and group. Here, we depict the relationship between $SD_{baseline}$ and post-intervention pain after adjusting for pre-intervention pain. In Placebo I, the no treatment group has a weak negative correlation; the placebo group's $SD_{baseline}$ is not correlated with post-intervention pain. In Placebo II, all groups demonstrate negligible correlations with $SD_{baseline}$.

Table 2: Relationships between baseline pain variability and relief by group.

		$\hat{\beta}$ **(CI)**	r_{sp} **(CI)**
Placebo I	No treatment (n = 20)	−1.0 (−2.1, 0.0)	−0.22 (−0.43, −0.02)
	Placebo (n=43)	1.2 (−0.1, 2.5)	0.22 (0.03, 0.42)
Placebo II	No treatment (n=11)	−0.2 (−1.3, 0.8)	−0.02 (−0.08, 0.02)
	Placebo (n=32)	0.0 (−1.2, 1.2)	0.00 (−0.07, 0.07)
	Drug (n=33)	0.0 (−0.8, 0.8)	0.00 (−0.10, 0.12)

Compatibility intervals (CI) are presented at the 95% level. $\hat{\beta}$ = unstandardized estimate from the marginal effect (expected change in post-intervention pain per unit increase in baseline pain SD), r_{sp} = semi-partial correlation coefficient.**DISCUSSION**

The purpose of this study was to quantify and isolate the relationship between baseline pain variability and post-intervention pain by group in two randomized, placebo-controlled clinical trials. Our work extends that of previous research by adjusting for the effects of regression to the mean and natural history via a no treatment control group (McDonald et al., 1983; Artus et al., 2010; O'Connell et al., 2015). By assuming that pain relief is a linear combination of natural history, regression to the mean, the placebo effect, and the drug effect,[1] we estimated the placebo- and drug-specific effects of $SD_{baseline}$ on post-intervention pain.

Contrary to previous work, we observed negligible correlations in our primary model, with $SD_{baseline}$ capturing $\lesssim 4\%$ of the variance in post-intervention pain across groups in both studies. Of principal interest was the placebo-specific effect, which previous studies suggest is on the order of $r \approx -0.3$. After adjusting for the no treatment group and pre-intervention pain, our placebo-specific estimates were incompatible with these previous estimates (**Table 1**). However, our results are consistent with the recent findings of Gillving et al. (2022), who observed negligible correlations between variability and improvements in patients who received placebo. Together, these results suggest that $SD_{baseline}$ may not be a strong, consistent, and "placebo"-specific predictor of pain relief across populations.

The magnitude and precision of our estimates were sensitive to modeling strategy. When modeling the groups separately, our effect estimates were larger and had greater variance, especially Placebo II. Thus, modeling the groups separately produced CIs that encompass previously reported estimates, but our point estimates were still relatively small and did not favor the placebo group. These results are suggestive that modeling differences may partly explain the discrepancy between studies. Similarly, differences in populations and sample sizes are important factors to consider (Harris et al., 2005; Farrar et al., 2014; Treister et al., 2019; Gillving et al., 2022).

Studies validating a $SD_{baseline}$-based prediction model are lacking. Nevertheless, the utility of $SD_{baseline}$ for trial exclusion is dubious. Even if $SD_{baseline}$ or some other variable was strongly predictive of pain relief following placebo, the removal of so-called "placebo responders" would also affect the active treatment group, especially since "placebo effects" are thought to be one component of the active treatment effects. Finally, although removing "placebo responders" would theoretically improve treatment effect estimates, the observed treatment effect for such a study would answer a different question since the sample is conditioned on $SD_{baseline}$. This may result in an optimistic, ecologically questionable estimate that may be unlikely to translate to the clinic.

Rather than trying to optimize treatment effect estimates in trials using peculiar exclusion criteria, researchers should optimize treatments and thus their effect estimates for the ecological

[1] Although additive assumptions are common, they are likely not true in the mechanistic sense (Kube and Rief, 2017). Yet, they may serve as reasonable first-degree approximations with high utility, allowing researchers to simplify their experiments (cf. full-factorial designs) and draw pragmatic conclusions.

patient population. After all, the goal of research is not to find large effects—it is to find large effects that will successfully translate and improve lives. Notwithstanding the limitations of conditioning on $SD_{baseline}$ for trial inclusion, since $SD_{baseline}$ may not be strongly predictive nor has it been validated as a prognostic variable, but is still able to capture variance in trial endpoints (Harris et al., 2005; Farrar et al., 2014; Treister et al., 2019), it may be well-advised to include as a covariate to improve statistical efficiency and estimates of treatment effects (Schelchter and Forsythe, 1985).

REFERENCES

Alexander, R.C., Raudibaugh, K., Spierings, E.L.H., and Katz, N. (2021). A 3-way Cross-over Study of Pregabalin, Placebo, and the Histamine 3 Receptor Inverse Agonist AZD5213 in Combination With Pregabalin in Patients With Painful Diabetic Neuropathy and Good Pain-reporting Ability. *Clin J Pain* 37**,** 38-42. doi: 10.1097/AJP.0000000000000886.

Artus, M., van der Windt, D.A., Jordan, K.P., and Hay, E.M. (2010). Low back pain symptoms show a similar pattern of improvement following a wide range of primary care treatments: a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 49**,** 2346-2356. doi: 10.1093/rheumatology/keq245.

DuMouchel, W. (Year). "Graphical Representations of Main Effects and Interaction Effects in a Polynomial Regression on Several Predictors", in: *Computer Science and Statistics: Proceedings of the 20th Symposium on the Interface*).

Dworkin, R.H., Turk, D.C., Peirce-Sandner, S., Burke, L.B., Farrar, J.T., Gilron, I., Jensen, M.P., Katz, N.P., Raja, S.N., Rappaport, B.A., Rowbotham, M.C., Backonja, M.M., Baron, R., Bellamy, N., Bhagwagar, Z., Costello, A., Cowan, P., Fang, W.C., Hertz, S., Jay, G.W., Junor, R., Kerns, R.D., Kerwin, R., Kopecky, E.A., Lissin, D., Malamut, R., Markman, J.D., McDermott, M.P., Munera, C., Porter, L., Rauschkolb, C., Rice, A.S.C., Sampaio, C., Skljarevski, V., Sommerville, K., Stacey, B.R., Steigerwald, I., Tobias, J., Trentacosti, A.M., Wasan, A.D., Wells, G.A., Williams, J., Witter, J., and Ziegler, D. (2012). Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 153**,** 1148-1158. doi: 10.1016/j.pain.2012.03.003.

Farrar, J.T., Troxel, A.B., Haynes, K., Gilron, I., Kerns, R.D., Katz, N.P., Rappaport, B.A., Rowbotham, M.C., Tierney, A.M., Turk, D.C., and Dworkin, R.H. (2014). Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: an ACTTION study. *Pain* 155**,** 1622-1631. doi: 10.1016/j.pain.2014.05.009.

Gillving, M., Demant, D., Holbech, J.V., Vase, L., Bach, F.W., Jensen, T.S., Finnerup, N.B., and Sindrup, S.H. (2022). Impact of variability in baseline pain on the placebo response in randomized, placebo-controlled, crossover trials in peripheral neuropathic pain. *Pain* 163**,** 483-488. doi: 10.1097/j.pain.0000000000002374.

Hall, K.T., Lembo, A.J., Kirsch, I., Ziogas, D.C., Douaiher, J., Jensen, K.B., Conboy, L.A., Kelley, J.M., Kokkotou, E., and Kaptchuk, T.J. (2012). Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. *PLoS One* 7**,** e48135. doi: 10.1371/journal.pone.0048135.

Harris, R.E., Williams, D.A., McLean, S.A., Sen, A., Hufford, M., Gendreau, R.M., Gracely, R.H., and Clauw, D.J. (2005). Characterization and consequences of pain variability in individuals with fibromyalgia. *Arthritis Rheum* 52**,** 3670-3674. doi: 10.1002/art.21407.

Katz, J., Finnerup, N.B., and Dworkin, R.H. (2008). Clinical trial outcome in neuropathic pain: relationship to study characteristics. *Neurology* 70**,** 263-272. doi: 10.1212/01.WNL.0000275528.01263.6c.

Khan, A., Detke, M., Khan, S.R., and Mallinckrodt, C. (2003). Placebo response and antidepressant clinical trial outcome. *J Nerv Ment Dis* 191**,** 211-218. doi: 10.1097/01.NMD.0000061144.16176.38.

Kube, T., and Rief, W. (2017). Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discov Today* 22**,** 729-735. doi: 10.1016/j.drudis.2016.11.022.

McDonald, C.J., Mazzuca, S.A., and McCabe, G.P., Jr. (1983). How much of the placebo 'effect' is really statistical regression? *Stat Med* 2**,** 417-427. doi: 10.1002/sim.4780020401.

O'Connell, N.E., Moseley, G.L., McAuley, J.H., Wand, B.M., and Herbert, R.D. (2015). Interpreting Effectiveness Evidence in Pain: Short Tour of Contemporary Issues. *Phys Ther* 95**,** 1087-1094. doi: 10.2522/ptj.20140480.

R Core Development Team (2020). "R: A language and environment for statistical computing". (Austria, Vienna: R Foundation for Statistical Computing).

Schelchter, M.D., and Forsythe, A.B. (1985). Post-hoc selection of covariates in randomized experiments. *Communications in Statistics - Theory and Methods* 14**,** 679-699. doi: 10.1080/03610928508828942.

Treister, R., Honigman, L., Lawal, O.D., Lanier, R.K., and Katz, N.P. (2019). A deeper look at pain variability and its relationship with the placebo response: results from a randomized, double-blind, placebo-controlled clinical trial of naproxen in osteoarthritis of the knee. *Pain* 160**,** 1522-1528. doi: 10.1097/j.pain.0000000000001538.

Tuttle, A.H., Tohyama, S., Ramsay, T., Kimmelman, J., Schweinhardt, P., Bennett, G.J., and Mogil, J.S. (2015). Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. *Pain* 156**,** 2616-2626. doi: 10.1097/j.pain.0000000000000333.

Vachon-Presseau, E., Abdullah, T.B., Berger, S.E., Huang, L., Griffith, J.W., Schnitzer, T.J., and Apkarian, A.V. (2021). Validating a biosignature predicting placebo pill response in chronic pain in the settings of a randomized controlled trial. *Pain*. doi: 10.1097/j.pain.0000000000002450.

Vachon-Presseau, E., Berger, S.E., Abdullah, T.B., Huang, L., Cecchi, G.A., Griffith, J.W., Schnitzer, T.J., and Apkarian, A.V. (2018). Brain and psychological determinants of placebo pill response in chronic pain patients. *Nat Commun* 9**,** 3397. doi: 10.1038/s41467-018-05859-1.

Link to full publication: https://doi.org/10.3389/fpain.2022.844309

Link to statistical analysis: https://github.com/siddharth-r-tiwari/pain-variability-and-relief

Email: sid.r.tiwari@gmail.com