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The impact of psychological factors on placebo responses in a randomized controlled trial comparing sham device to dummy pill

Suzanne M. Bertisch, M.D., M.P.H.[1,2], **Anna R. T. Legedza, Sc. D.**[3], **Russell P. Phillips, M.D.**[1,2], **Roger B. Davis, Sc. D.**[1,2], **William B. Stason, M.D., M.S.**[4], **Rose H. Goldman, M.D., M.P.H.**[5], and **Ted J. Kaptchuk**[1,2]

[1]Division for Research and Education in Complementary and Integrative Medical Therapies, Osher Institute, Harvard Medical School, Boston, Massachusetts

[2]Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

[3]Vertex Pharmaceuticals, Cambridge, MA

[4]Center for the Analysis of Health Practices, Harvard School of Public Health, Boston, MA

[5]Division of Occupational & Environmental Medicine, Cambridge Health Alliance, Cambridge, MA

Abstract

Objectives—To explore to what extent psychological factors such as expectation, depression, anxiety, and belief in alternative medicine impact placebo response and differential responses to separate placebo interventions.

Methods—We analyzed data from a randomized controlled trial designed to compare the clinical response of two distinct placebo treatments (sham acupuncture device and placebo pill) in 119 participants with persistent distal upper arm pain due to repetitive stress injury (RSI). We used a multivariable linear regression model to identify potential correlates of self-reported upper extremity pain at the end of treatment in both placebo arms of the study combined. We also performed stratified analyses by placebo treatment.

Results—We did not find any of the psychological factors of interest to be associated with pain at the end of treatment in our combined analysis. We found higher baseline pain score and pain for longer than one year's duration to be significantly associated with higher pain scores at the end of treatment for the placebo treatments combined. In stratified analyses, for the sham acupuncture group, we found higher baseline depression score, higher baseline pain score, and younger age to be independently correlated with higher pain score at the end of treatment. For the placebo pill group, only baseline pain was significantly correlated to pain score at end of treatment.

Corresponding Author and Requests for Reprints: Suzie Bertisch, MD, MPH, Division for Research and Education in Complementary and Integrative Medical Therapies, Harvard Medical School, 401 Park Drive, Suite 22-A West, Boston, Massachusetts, 02215. Telephone Number (617) 384-8552; Fax Number (617) 384-8555. Suzannne_Bertisch@hms.harvard.edu.

Conclusion—In this trial, neither expectancy nor psychological states were associated with response to placebo, with the exception of baseline depression score for the sham acupuncture arm.

Keywords

Repetitive Stress Injury; Placebo; Sham Acupuncture; Expectancy; Depression

Introduction

Placebo effects are controversial. (1) While recent physiological evidence has impressively demonstrated that “mental events induced by placebo administration can activate mechanisms that are similar to those activated by drugs” (2) other evidence, including meta-analysis, has suggested that the placebo effect is minimal or even non-existent. (3) We recently completed a randomized controlled trial comparing two placebos designed to compare the differential clinical responses of two different placebo rituals in participants with persistent distal upper arm pain due to repetitive stress injury (RSI), and found the sham device had greater effects than the placebo pill on self reported pain over the entire course of treatment (−0.33 (−0.40 to −0.26) v −0.15 (−0.21 to −0.09), p-value < 0.001).(4)

Since the medical recognition of a placebo response, there has been great interest in predictors of response. The most common method for investigating clinical placebo responses has been to use a secondary data analysis strategy in which baseline demographic or psychological characteristic of participants in pharmacologic randomized controlled trials are correlated with responses to placebo. These efforts have been extensive and the conclusion of the most recent review of these efforts has been: “many variables were identified as being associated with placebo effects, but there was little or no agreement [between trials] about which variables contributed…[and correlations] could not be replicated” when the same methodology is again applied (5, Shapiro and Shapiro, 1997) Early reviews had similar findings. (7–10)

More recently expectation has been considered an especially likely predictor of placebo response. (11–13) Multiple papers have been published looking to correlate expectancy with outcome. (14) While many papers have demonstrated a correlation (15,16), an absence of correlation has not been uncommon. (17, 18) Because our study compared two different placebos, we thought our database would be a valuable data source to examine the contribution of measures of expectancy and other psychological variables to response to placebo treatment overall and to different types of placebos.

Methods

Data Source

We analyzed data from a randomized clinical trial designed to compare the clinical response of two distinct placebo interventions (placebo pill and sham acupuncture) in participants with persistent (≥3 months duration) distal upper arm pain due to repetitive stress injury (RSI).(4) Two hundred and seventy participants were initially randomized to receive either a

validated sham acupuncture device or oral placebo pill during the placebo run-in phase of the trial. At two weeks, participants underwent secondary randomization to: continue their current placebo treatment (n=119); real acupuncture (n=59); or amitriptyline (n=59). We considered the 119 participants who received sham acupuncture (n=60) or placebo pill (n=59), for 6 and 8 weeks respectively, as our study population. The nested sub-study comparing genuine acupuncture and amitriptyline to their respective placebo was performed for ethical reasons and was not considered the primary study. Details of this study have been previously published(4), and Figure 1 illustrates the study's schema.

Outcomes of Interest

We defined our primary outcome as self reported intensity of pain in the most severely affected arm measured on a 10-point numerical scale ranging from no pain (1) to most severe pain imaginable (10) at the end of treatment (6 or 8 weeks).

Baseline Psychological Factors

We considered several baseline psychological factors to be potential correlates of pain score at the end of treatment, including participants' expectation of pain score, depression, anxiety, and participant beliefs in effectiveness of alternative medicine, acupuncture, and conventional medicine. We defined expectancy using the participants' baseline response to the question that pertained to their assigned treatment group: "Rate how intense you think the pain or discomfort will be 2 weeks from now if you are assigned to (acupuncture or medication)?". We defined depression using the scores on the Center for Epidemiologic Studies Depression Scale (CES-D) (0–60 range, higher scores indicating more symptomatology) measured at baseline, and we defined anxiety using the Psychological General Well-Being Schedule anxiety sub-score (3–18 range, lower scores indicating more symptoms), also measured at baseline. Strength of belief in the effectiveness of complementary and alternative medicine, acupuncture, and traditional medical therapy were also ascertained at baseline. At baseline, we asked participants "How effective overall do you believe each of the following type of treatment is…acupuncture; alternative medicine overall; traditional medicine overall" (1–5 range, higher scores indicating more effectiveness).

Additional Factors of Interest

Additionally, we considered sociodemographic characteristics such as age, sex, race (white, non-white), and educational attainment (≥4 years of college, < 4 years of college), and clinical status to be potential correlates of self-reported pain score at the end of treatment. As a measure of participants' clinical status, we used data on clinical diagnosis of arm pain (tendonitis/epicondylitis, neuropathic pain/other), self reported intensity of arm pain at baseline (1 to 10, higher score=more pain), and duration of symptoms (3–12 months, >1 year).

Statistical Analyses

We performed descriptive statistics to characterize the study. We used Spearman correlations for our continuous predictors and Student's t-tests for our normally distributed

variables to identify potential correlates of the primary outcome, self-reported intensity of pain at end of treatment. Given the small sample size of some of the potential correlates of interest, we performed sensitivity analyses using Wilcoxon rank sum tests for the binary predictors.

To identify the factors associated with end treatment pain scores, we created a multivariable linear regression model using variables with a p-value of <0.20 on bivariable analyses. We used a forward selection process and only conditions with a Wald statistic p-value ≤ .05 were retained in our final model. We then performed pre-specified stratified analyses, repeating these methods of creating multivariable models for each randomization group to explore the potential correlates of end treatment pain score specific to each placebo treatment. Given the reduced sample sizes for our stratified multivariable models, in addition to using variables with a p-value of <0.02 on stratified bivariable analyses, we also used variables considered for inclusion in the combined treatment model, which had similar correlations in stratified bivariable analyses. For example, baseline anxiety had a similar correlation in both combined and stratified analyses, and thus was considered for inclusion into each multivariable model.

We performed sensitivity analyses to examine the potential confounding effect of our main variables of interest whose sample sizes precluded their initial inclusion in our main model (i.e. belief in the effectiveness of acupuncture). We defined confounding by a change of 10% or more in the estimated β-coefficient for the other variables of interest.

Results

Table 1 details the psychological and clinical characteristics of our study population. Overall, the participants' tended to be white, well-educated, and had upper extremity pain for greater than one year's duration. Baseline mean pain score reflected moderate levels of pain, and the mean expected pain score in 2 weeks on assigned treatment was 1.6 points lower than baseline pain scores. Baseline mean depression and anxiety scores reflected low symptomatology, and participants had a stronger belief in the effectiveness of acupuncture compared to conventional therapy. The sham acupuncture and placebo pill groups did not differ in their baseline characteristics. Over the course of treatment, mean scores decreased by more than one point, representing a small but clinically meaningful decrease in pain score in both groups.

Tables 2 and 3 depict the associations between the continuous and binary variables of interest and self-reported pain score at end of treatment, respectively, by combined and individual treatment groups. For the treatment groups combined, we considered baseline pain score, expectancy, baseline anxiety, gender, and symptom duration for inclusion in our multivariable model.

In our primary multivariable model, we found higher baseline pain score (β-coefficient=0.43, p<0.0001) and duration of pain for more than one year (β-coefficient=0.74, p=0.04) to be associated with higher pain score at the end of treatment, explaining 17.0% and 3.1% of the variability respectively. Patient expectation, baseline depression score,

baseline anxiety score, and belief in the effectiveness of acupuncture, traditional, or complementary medicine did not correlate with pain score at the end of treatment.

In our stratified analyses, we identified different correlates of the end treatment pain score for the sham acupuncture compared to the placebo pill group. In our multivariable model, for the sham acupuncture arm, we found higher baseline pain (β-coefficient=0.81, $p<0.0001$), higher baseline depression score (β-coefficient=0.08, $p=.02$), and younger age (β-coefficient= −0.05, $p<0.01$) to be correlated with higher pain scores at the end of treatment. Taken together these correlates accounted for 39.6% of the variability. Baseline pain alone explained 23.9% of the variability, and baseline depression and age explained 7.5% and 8.2% of the variability respectively. For the placebo pill intervention, only baseline pain was associated with pain score at the end of treatment (β-coefficient=0.44, $p<0.01$) and explained 12.5% of the variability. Participant expectation of pain score at 2 weeks on assigned treatment was not a significant independent predictor of pain at end treatment for either placebo intervention. Likewise, we found no association between the sociodemographic factors (sex, race, and educational attainment) and end of treatment pain scores in either arm. Our results did not change with our sensitivity analyses.

Discussion

Our parent study showed placebo responses and, in fact, differential placebo effects for pain, with the sham acupuncture arm conferring a greater reduction in pain score. (4) Placebo response is a complex phenomenon and we undertook this exploratory study to investigate the potential psychological and clinical features that might account for placebo responses, and characteristics unique to differential placebo effects. We found that only baseline pain and duration of symptoms were significant correlates for end treatment pain scores when we combined the participants receiving placebo treatment. Additionally, we found baseline pain to be independently correlated with end treatment pain in our stratified analysis; however, baseline depression scores and age were also significant correlates of end treatment pain scores in the sham acupuncture group, but not in the placebo pill group.

To our surprise, we did not find participant expectancy to correlate with end treatment pain scores in either our combined or stratified analysis. Furthermore, we also found no relationship between participant strength of belief in the assigned treatment group and pain scores at the end of treatment in either placebo group. Previous research examining the role of patient expectation and the placebo response has been mixed. Patient expectancy is a complex phenomenon, encompassing both psychological states and contextual factors, and likely varies throughout the course of therapy. Qualitative research has demonstrated that expectancy is not a stable trait and continually shifts during a randomized controlled trial. (19) Thus patient expectancy may be difficult to measure, particularly with a single question asked at one point in time. Our results suggest more research is needed to better define this complex cognitive state before its role in placebo response can be definitively determined.

Interestingly, we found differing correlates of end treatment pain scores between the sham acupuncture and placebo pill groups (i.e. baseline depression score and age), suggesting that different factors may play a role in improvement of pain scores in patients receiving

different placebo treatments. Though our findings are consistent with previous research estimating that 25–60% of patients with depression that are treated with placebo may have substantial reductions in symptoms (20, 21) our results suggest that patients with depression may possibly be more likely to respond to sham acupuncture compared to placebo pills.

We found baseline pain score to be the strongest predictor of pain score at the end of treatment, which supports the concept that baseline pain should be accounted for in clinical studies examining the effectiveness of a therapeutic intervention, through stratified randomization or adjustment in a multivariable model. Without systematically accounting for baseline pain scores, no distinction can be made between interventional efficacy, regression to the mean, or natural history of a disease. In our study, since we did not have a natural history arm and baseline pain was a significant correlate of pain outcomes in both treatment groups, we cannot comment on the impact baseline pain score may have on the placebo response.

We were surprised by the almost total absence of correlation between placebo response and pencil and paper measures of psychological variables. In this study, placebo response was not configured by any single such factor. We speculate that the placebo effect is not a simple psychologically determined response but instead represents a mind-body interaction that includes within-person variability of biomarker levels and psychological states, individual factors such as genotype, psychological traits, social and behavioral attributes and macro-level contextual factors ranging from characteristics of the local social network to those of larger social-environmental and cultural-meaning contexts. Looking for one-to-one correlations may be too simplistic.

Our study has several important limitations. First, our main study was not able to account for the natural history of RSI, and thus we cannot determine to what extent our measured placebo responses represent responses beyond regression to the mean and the natural variability of the illness, and whether our results reflect the natural history of RSI or the placebo response. Additionally, RSI is a composite of many illnesses such as epicondylitis, carpal tunnel syndrome, and neuropathic pain, and differing placebo effects might occur in different clinical populations. Furthermore, as mentioned, our factors of interest were mainly limited to pen and pencil measurements at baseline and do not reflect “a composite experience” that enmeshes both the healing experience and the placebo response over time.

In this study we did not identify associations between psychological and socio-demographic variables and response to placebo intervention. We speculate that placebo responses detected in this trial were a composite of interactions on psychological, social, cultural and biological variables.

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Table 1

Sample Sociodemographic, Psychological, and Clinical Characteristics, Combined and by Placebo Treatment

	Subjects Receiving Placebo Treatment	Placebo Pill	Sham Acupuncture
Sample Size	119	59	60
Age in years, mean (s.d.)	38.2 (11.2)	38.9 (11.6)	37.5 (11.0)
Female (%)	51	49	53
White race (%)	81	78	83
At least 4 years of college (%)	78	75	82
Diagnosis of tendonitis or epicondylitis (%)	66	66	67
Symptoms >1 year duration (%)	66	64	67
Baseline CES depression score, mean (s.d.)	9.6 (6.9)	9.6 (6.9)	9.6 (7.1)
Baseline Anxiety score, mean (s.d.)	13.2 (2.7)	13.1 (2.8)	13.3 (2.7)
Belief in effectiveness of CAM, mean (s.d.)*	3.1 (1.1)	3.1 (1.2)	3.1 (1.1)
Belief in effectiveness of acupuncture, mean (s.d.)*	3.8 (0.9)	3.8 (0.9)	3.8 (0.9)
Belief in effectiveness of conventional medicine, mean (s.d.)*	3.1 (1.0)	3.2 (1.0)	3.0 (0.9)
Baseline pain score, mean (s.d.)	5.2 (1.5)	5.1 (1.6)	5.4 (1.4)
Expected pain score in 2 week on assigned treatment, mean (s.d.)	3.6 (1.5)	3.6 (1.6)	3.6 (1.4)
Pain score at end of treatment, mean (s.d.)	3.8 (1.9)	3.9 (1.9)	3.6 (1.9)

s,d.=standard deviation

*Sample size<100 for combined analysis

Table 2

Spearman correlations Between Continuous Variables and Self-reported Pain Score at End of Treatment

	Combined Treatments		Placebo Pill		Sham Acupuncture	
Variable	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Age (years)	−0.11	0.21	−0.02	0.91	−0.19	0.13
Baseline pain	0.37	<0.001	0.33	0.01	0.44	<0.001
Baseline expectation of pain score at 2 weeks on assigned treatment	0.19	0.04	0.22	0.12	0.17	0.19
Baseline CES-Depression Scale	0.08	0.38	−0.04	0.79	0.17	0.20
Baseline Anxiety	−0.13	0.15	−0.1	0.44	−0.16	0.23
Belief in effectiveness of CAM[†*]	0.06	0.59	0.02	0.91	0.08	0.58
Belief in effectiveness of acupuncture[*]	0.01	0.95	−0.29	0.08	0.29	0.15
Belief in effectiveness of conventional medical therapy	0.01	0.91	−0.002	0.98	0.01	0.96

r= correlation coefficient

[†]CAM=Complementary and Alternative Medicine

[*]Sample size < 50

Table 3

Associations between binary variables and self-reported pain score at end of treatment for combined placebo treatment

	Combined Treatments			Placebo Pill			Sham Acupuncture		
Characteristic	**Sample Size**	**Mean (S.D.)**	**p-value**	**Sample Size**	**Mean (S.D.)**	**p-value**	**Sample Size**	**Mean (S.D.)**	**p-value**
Gender									
Male	58	4.1 (2.1)	0.07	29	4.1 (2.0)	0.40	32	4.0 (2.1)	0.1
Female	61	3.4 (1.7)		30	3.0 (1.8)		28	3.2 (1.6)	
Race									
White	96	3.9 (2.0)	0.35	46	4.1 (2.0)	0.30	50	3.7 (2.0)	0.81
Non-white	23	3.4 (1.6)		13	3.4(1.7)		10	3.5(1.6)	
Education									
≥ 4 years of college	93	3.8(2.0)	0.42	44	3.9 (1.9)	0.73	49	3.8 (2.0)	0.09
< 4 years of college	26	2.8 (1.8)		15	4.1 (1.9)		11	2.7 (1.3)	
Diagnosis									
Epicondylitis/Tendonitis	79	3.6 (1.9)	0.23	39	3.8 (2.0)	0.70	40	3.4 (1.8)	0.2
Neuropathic /Other	40	4.1 (2.0)		20	3.2 (1.8)		20	4.1 (2.2)	
Symptom Duration									
3–12 months	41	3.4 (2.0)	0.14	21	3.5 (2.1)	0.20	20	3.6 (2.0)	0.43
> 1 year	78	4.0 (1.9)		38	4.2 (1.8)		40	3.8 (1.9)	

S.D.= Standard Deviation