Enhancing Subjects' Awareness of Key Placebo Response Factors: The Importance of Implementing a Brief Educational Placebo Response Video

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ABSTRACT

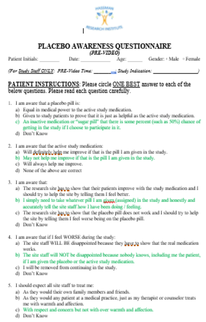
Introduction: The placebo effect continues to plague Central Nervous System (CNS), addiction, and general medicine clinical trials (Enck et al., 2011) and to be muting the potential pharmacological efficacy of new drugs. Weber et al. (2005) identified a plethora of factors that contribute to this effect, including site-subject interactions, subject expectations of benefit, lack of subject understanding of the placebo, and subject uncertainty of his/her role in the trial. The current study takes an important step in understanding how subjects can be educated about these key factors which ultimately may lead to reducing their response to the placebo. **Methods:** This pilot study implemented a pretest-posttest randomized control group design. Subjects first signed the Informed Consent Form at the Screening Visit per their CNS, addiction, or general medicine placebo-controlled clinical trial. They then completed the Placebo Awareness Questionnaire (PAQ) containing 5 multiple choice questions (one correct answer per item) to assess subjects' awareness of the key factors related to the placebo response. Upon completion of the PAQ, subjects were randomly assigned to the control or intervention (video) group. Subjects in the intervention group immediately then watched a seven-minute educational video that addressed the factors identified by Weber et al. (2005). At the conclusion of the video, intervention participants completed the same PAQ without access to the first responses. To match the temporality of the experimental group, the control subjects completed the PAQ seven minutes after completing the first PAQ, and to ensure the video intervention and its potential lessons were not withheld from the control subjects they watched the video after completing the post-test PAQ. **Results:** A comparison of the intervention and control groups by age/gender showed no statistical differences. After testing for normality, a repeated measures one-way analysis of variance (ANOVA) was calculated to assess between- and within-group differences of the intervention and control groups. The results indicated that there is a significant difference, $F(2, 41) = 700$, $p < .001$, between the intervention group and the controls, such that the intervention group was significantly better able to identify the factors (i.e., their role) associated with reducing a placebo response after watching the video as compared to the control group. Moreover, a Wilcoxon signed rank test indicated significant differences between the pretest and posttest intervention group ($V=325$, $p<.001$) suggesting again that the intervention helped subjects learn the appropriate placebo response factors, whereas the control group showed no statistical difference between their pretest and posttest ($V=77.50$, $p=.101$). **Conclusions:** Despite having read and confirmed understanding by research site staff of the Informed Consent Form, subjects across the three different placebo-controlled study indications did not fully understand all of the key factors associated with the placebo response. However, the results indicated that subjects who watched a brief video addressing these factors had significantly greater awareness of the issues that affect the placebo response as compared to subjects who did not watch the video. Research sites and perhaps even rater training vendors are encouraged to implement such a program before subjects participate in their placebo-controlled trials. Further studies should be conducted for replicability purposes and suggestions for future studies are presented in the poster (e.g., does the current educational intervention actually influence placebo response in the clinical trial).

INTRODUCTION

- The high rate of placebo effect, approximately 50% across CNS study indications, continue to bewilder the pharmaceutical industry (Enck et al., 2008; Kemp et al., 2010).
- While various methodological strategies have been implemented or recommended to reduce the placebo effect (e.g., centralized ratings, remote rater monitoring, lessening assessment duration, subject duration of current illness exacerbation, and different lead-in phase procedures), evidence indicates a persistent significant downward trend in recent decades concerning drug-placebo separation (Papakostas & Fava, 2009; Potkin et al., 2011) with a profound risk for Big Pharma losing $2.5 Billion per new drug (Mullin, 2014).
- Research has been arguably scarce in directly targeting how potential interventions specifically aimed at subjects (one of the clear sources of the placebo effect) may help minimize study participants' response to placebo. Interventions focused on educating subjects about the key factors which are commonly cited (Alphs et al., 2012; Weber et al., 2005) to cause the placebo effect (below list) is warranted.
  - ❖ **Site-subject interactions**
  - ❖ **Subject expectations of benefit**
  - ❖ **Lack of subject understanding of the placebo**
  - ❖ **Subject uncertainty of his/her role in the trial**
- The current study examines if subjects initially understand the above factors linked to a placebo response and how one strategy (having subjects watch a brief psychoeducational video about the factors) may help improve subjects' understanding.

METHODS

- This study implemented a pretest-posttest randomized control group design, as described below.
- Subjects first signed the Informed Consent Form (ICF) at the Screening Visit per their respective CNS, addiction, or general medicine placebo-controlled clinical trial.
- Subjects then completed the Placebo Awareness Questionnaire (PAQ) containing 5 multiple choice questions (one correct answer per item) to assess subjects' awareness of the key factors related to the placebo response.



PLACEBO AWARENESS QUESTIONNAIRE
(PRE-VIDEO)

Patient Initials: _____ Date: _____ Age: _____ Gender: ○ Male ○ Female

(For Study Staff ONLY: PRE-Video Time: _____; Study Indication: _____)

PATIENT INSTRUCTIONS: Please circle ONE BEST answer to each of the below questions. Please read each question carefully.

1. I am aware that a placebo pill is:
   a) Equal to medical power to the active study medication.
   b) Given to study patients to prove that it is just as helpful as the active study medication.
   c) An inactive medication or "sugar pill" that there is some percent (such as 50%) chance of getting in the study if I choose to participate in it.
   d) Don't Know

2. I am aware that the active study medication:
   a) Will always help me improve more than that in the pill I am given in the study.
   b) May help me improve if that is the pill I am given in the study.
   c) Will always help me improve.
   d) None of the above are correct

3. I am aware that:
   a) The research site may show that their patients improve with the study medication and I will be disappointed if I am given the placebo pill.
   b) I simply need to take whatever pill I am given (assigned) in the study and honestly and accurately tell the site staff how I have been doing / feeling.
   c) The research site may show that the placebo pill does not work and I should try to help the site by telling them I feel worse being on the placebo pill.
   d) Don't Know

4. I am aware that if I feel WORSE during the study:
   a) The site staff WILL BE disappointed because they may show that the trial medication is working.
   b) The site staff will NOT be disappointed because nobody knows, including me the patient, if I am given the placebo or the active study medication.
   c) I will be removed from continuing in the study.
   d) Don't Know

5. I should expect all site staff to treat me:
   a) As they would their own family members and friends.
   b) As they would any patient at a medical practice, just as my therapist or counselor treats me with warmth and affection.
   c) With respect and concern but not with over warmth and affection.
   d) Don't Know

Figure 1: Placebo Awareness Questionnaire (PAQ; green font are correct answers shown for purposes of the poster.

- The PAQ was developed specifically for this study to ascertain subject knowledge about the key placebo response factors (see left side **Figure 1**).
- Upon completion of the PAQ, subjects were randomly assigned to the Control or Intervention (video) Group.
- Subjects in the Intervention Group immediately watched a 7-minute educational video after completing the Pre-Test PAQ. The video covered the subject key placebo response factors commonly identified within the literature (e.g., Weber et al., 2005).
- At the conclusion of the video, Intervention Group participants completed the Post-Test PAQ without access to the first responses.
- The order of the Post-Test PAQ questions were changed to avoid response bias and ensure subjects read each question carefully (Rubin, 2005).
- To match the temporality of the experimental group, the Control Group subjects completed the Post-Test PAQ seven minutes after completing the first PAQ
- Control Group subjects did watch the placebo response video after completing the Post-Test PAQ to ensure the video intervention and its potential lessons were not withheld from any study subjects.

RESULTS

- There were 25 subjects within each of the Intervention and Control Groups (N = 50) and a Friedman rank sum test indicated no statistical differences by age/gender between these groups.
- After testing for normality, a repeated measures one-way analysis of variance (ANOVA) was calculated (see **Table 1**), indicating there was a significant difference, $F(2, 41) = 700$, $p < .001$, between the Intervention Group and the Controls, such that the Intervention Group subjects were significantly better able to identify the factors (i.e., their role) associated with reducing a placebo response after watching the video as compared to the Control Group participants.
- **Figure 2** illustrates the ANOVA based statistically significant mean differences between the Pre-Test and Post-Test Intervention and Control Group subjects (respectively [with Standard Deviations], 32.04 [4.14], 88.64 [8.96], 31.76 [3.49], 30.80 [2.18]).
- A Wilcoxon signed rank test indicated significant differences between the Pre-Test and Post-Test Intervention Group ($V=325$, $p<.001$), suggesting again that the video intervention helped subjects learn the appropriate placebo response factors, whereas the Control Group subjects showed no statistical difference between their Pre-Test and Post-Test ($V=77.50$, $p=.101$).
- After a Friedman rank sum test was conducted, $\chi2(3) = 49.62$, $p < .001$ (indicating the differences in the median values of the Intervention and Control Group Pre- and Post-Tests were statistically significant), a pairwise comparison was examined between each variable level to further explore the potential impact of having subjects watch the placebo response video. **Figure 3** shows the significant differences between the pairwise comparisons, indicating that subjects learned more about the four placebo response factors as a result of the intervention (i.e., watching the video).

RESULTS

Source	*df*	*SS*	*MS*	*F*	*P*
Within Factor	2	61168.11	35666.29	700	<.001
Residuals	42	2095.64	50.91		

Table 1: Repeated Measures ANOVA for Pre-Test and Post-Test Intervention and Control Groups

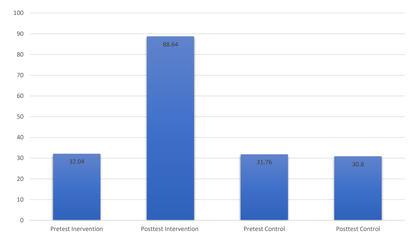


Figure 2: ANOVA based statistically significant mean differences between the Pre-Test and Post-Test Intervention and Control Group subjects

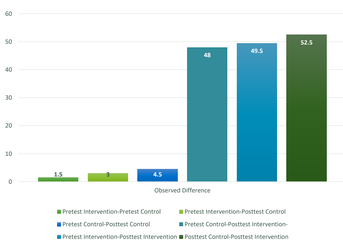


Figure 3: Pairwise Comparison for the Mean Ranks of the Pre- and Post-Test Intervention and Control Group Subjects showing the Observed Difference

CONCLUSIONS

- Theories abound regarding the ways in which subjects contribute to the placebo effect – notably the commonly cited factors of: their interactions with site staff, expectations of benefit, lack of subject understanding of the placebo, and subject uncertainty of his/her role in the trial.
- To our knowledge, the current study is the only one which empirically examines how subjects initially are naïve about the above key subject-centered placebo contributing factors and how they may best be educated to enhance their awareness about these factors.
- **The results of the study indicated that subjects were less than clear about the factors which are commonly cited as contributing to the placebo effect in clinical trials and that a brief (7-minute) psychoeducational video focused on these factors significantly increased subjects' understanding of these crucial issues.**
- Given that the placebo response factors are centered around subject expectations during a clinical trial, the current results add to the literature concerning the role in which expectations have in generating a placebo effect. For example, Lidtsone et al.'s (2010) seminal publication found that the strength of PD subject expectations for improvement (even though all subjects were blindly given a placebo) predicted increased dopamine release (i.e., reward circuitry) in the ventral striatum and subjects also reported feeling better. The current study results indicate that indeed subject expectations can be managed/harnessed through a brief video regarding the placebo effect in clinical trials.
- The limitations of the current investigation include: (a) the study does not address whether subjects' increased knowledge about the placebo effect key factors translates to greater drug-placebo separation; (b) It is unknown if subjects remember the placebo response key factors throughout their participation in trials (although some sites have begun to read a script explaining these factors to each study subject per study visit which should extend their understanding throughout the trial); and (c) it is unknown if subjects in this current study who were participating in different indication clinical trials (e.g., CNS vs Medical) were more likely to learn the key factors. Future studies should address these matters.
- **The results of the study are even more vital considering that subjects had agreed to participate in a placebo-controlled clinical trial (i.e., subjects read their study's ICFs before participating in the current investigation). Given that many current ICFs do not detail the key placebo response related factors, it is RECOMMENDED that research sites or sponsors implement a video or similar method (e.g., script read to subjects by raters) to ensure subjects at the outset of their participation clearly understand their role and the expectations of participating in a placebo-controlled study which are intended to reduce their potential biased symptom reporting.**

References provided on reverse side of poster handout.