HRI Science Division

The Power of an Educational Placebo Response Video: Strengthening Subject Placebo Response Awareness Across Demographic Variables and Diagnoses

Howard Hassman, DO, Elan A. Cohen, Ph.D., Kimberley A. Myers, EMBA, Shawn Hossain, DO, Ashok V. Joseph, MD, and Jaclyn M. Lobb, MS

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ABSTRACT

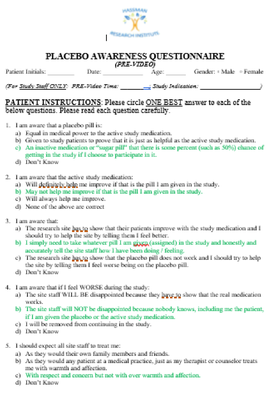
Introduction: The clinical trial industry continues to grapple with increasing placebo responses (Kemp et al., 2010; Kirsch, 2016). One technique which merits empirical exploration is educating subjects on factors linked to their potential increased response to the 'inert' substance (Weber et al., 2005). These factors include site-subject interactions, subject expectations, lack of subject understanding of the placebo, and subject role uncertainty. The current study investigates whether an educational video can raise subjects' awareness about these factors across gender, age, and diagnostic indication, which ultimately may lead to reducing subjects' response to the placebo. **Methods:** Patients with a diagnosis of schizophrenia, depression, substance use, or general medicine completed a Placebo Awareness Questionnaire (PAQ) to assess awareness of the placebo response key factors. Upon completion of the PAQ, subjects were randomized to the Intervention Group (IG; n = 100) where they watched a seven-minute video regarding these factors, with completion of a post-PAQ. Control group subjects (CG; n = 100) completed the PAQ without watching the video. **Results and Conclusion:** A repeated measures ANOVA showed a significant difference between the IG and the CG such that the IG subjects were better able to identify the placebo response factors after watching the video ($p < .001$). Secondary analysis indicated this finding was true across gender, age, and diagnoses (all $p < .05$ except for the 20-29 age group). Within-group analyses suggested a differential effect of the intervention on the subgroups (e.g., IG females scored higher than IG males post video). Implications of these findings will be discussed.

INTRODUCTION

- The placebo effect's profusion within the clinical trial industry can only be viewed as a plague with accompanying insidious consequences. This assertion stems from the slightly more than 50% failure rate between psychiatric drugs and placebo (Greenberg, 2003; Khan et al., 2002; Kirsch, 2016; Mitte et al., 2005) and that 30-40% of subjects on placebo participating in medically oriented studies report significant improvement (Hrobjartsson & Gotzsche, 2001).
- The robustness of the placebo response in clinical trials and other research ventures (e.g., academic) transcends across a wide range of illnesses, including schizophrenia (Kemp et al., 2010; Kinon et al., 2011), depression (Dworkin et al. 2005; Rutherford & Rose, 2013), anxiety (Mitte et al., 2005), bipolar mania (Yildiz et al., 2011), heart failure (Olshansky, 2007), cardiovascular (Wechsler et al., 2011), pain (Benedetti et al. 2007), migraines (Eikermann & Diener, 2003), and motor disorders (Benedetti et al., 2007).
- 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 the placebo effect is only increasing as time progresses (Kemp et al., 2010; Loebel et al., 2010) 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 there is variability among subjects' gender, age, and diagnostic indication regarding their initial understanding of the above placebo response factors and if subjects' understanding differs among these variables after being exposed to a brief psychoeducational video about these crucial factors.

METHODS

- This study implemented a pretest-posttest randomized control group design, as described below.
- Subjects completed the site's consent to treat paperwork and were diagnosed by qualified site staff with either schizophrenia, current major depressive episode (MDE), substance use disorder (addiction), or general medicine (diabetes, pain, or headaches).
- 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 in 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 30%) 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 definitely help me improve if that is the pill I am given in the study.
   b) May not 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 has to show that their patients improve with the study medication and I should try to help the site by telling them I feel better.
   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 has to 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 have to show that the real medication works.
   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 ever 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 Pre-Test PAQ, subjects were stratified based on indication, age, and gender and were randomly assigned to the CG or IG (video) in a 1:1 ratio to ensure each group had an equivalent sample of these features.
- Subjects in the IG 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., Bensing & Vaerheul, 2010; Weber et al., 2005).
- At the conclusion of the video, IG 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 CG subjects completed the Post-Test PAQ seven minutes after completing the first PAQ
- CG 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 a total of 200 subjects (see **Table 1** for subgroup sample size)

Gender	IG	CG	Age	IG	CG	Diagnosis	IG	CG
Female	50	50	**20-29**	25	25	**MDE**	25	25
Male	50	50	**30-39**	25	25	**Schizophrenia**	25	25
			40-49	25	25	**Addiction**	25	25
			50 and Up	25	25	**General Medicine**	25	25
Total	100	100		100	100		100	100

Table 1: Study sample size by experimental group and gender, age, and diagnostic category

- A Friedman rank sum test indicated no statistical differences by gender/age between the IG and CG.
- After testing for normality, a repeated measures one-way analysis of variance (ANOVA) was calculated (see **Table 2**), indicating there was a significant difference ($p < .001$), between the IG and CG overall and across all subgroups (except the 20-29 age sample; $p = .22$), such that the IG 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 CG.
- As expected, the CG Pre- and Post-Test means were not significantly different across all subgroups and when all groups were combined (Pre-Test $M = 29.6$; Post-Test $M = 35.51$; $p=.61$). This finding, as well as the CG and IG comparison results, provides further evidence that the video was effective in educating subjects about the placebo response factors (see **Figure 2,** illustrating PAQ improvement in the IG overall and by subgroup).
- The IG and CG Pre-Test scores were not statistically different and this maintained across all subgroups, indicating that all subjects had similarly poor understanding about the key placebo response factors.
- Although not significantly different, Post-Test IG females scored higher ($M=86$) than their male counterparts ($M=68$) by 18 points (see Conclusion Section).

RESULTS

ANOVA	*p*
ALL	<0.001
MDD	<0.001
Schizo	<0.001
Addiction	<0.001
GM	<0.001
20-29	0.22
30-39	<0.001
40-49	<0.001
50 and Up	<0.001
Female	<0.001
Male	<0.001

Table 2: Repeated Measures One-Way ANOVA *p*-values representative of Pre- and Post-Test Intervention versus Control Groups Means

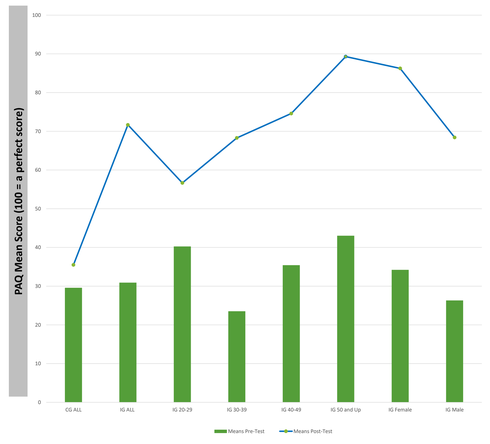


Figure 2: PAQ Mean Score (where 100 = a perfect score) Comparisons Between the Pre- and Post-Test Subjects Overall and by Subgroups

CONCLUSIONS

- Our thorough review of the literature revealed that the current study is the only one which empirically examines potential differences between gender, age, and diagnostic indications in relation to subjects' understanding of the commonly cited factors known to influence placebo response in clinical trials.
- **The results of the study indicate that subjects were quite naïve about the placebo response factors and this held true across gender, age, and diagnostic categories. However, the results are encouraging because they indicate that a brief (7-minute) psychoeducational video focused on these factors significantly increased subjects' understanding of these crucial issues no matter what gender, age (exception within the 20-29 age group), and diagnoses tested in the current investigation.**
- Learning style and attention theories may provide a critical explanation for why the Post-Test IG 20-29-year-old subgroup did not score significantly better than the Post-Test CG of that same age group, although it is noteworthy that the IG scored higher by 27.5 points. **The study's 20-29-year-olds represented an amalgam of Generations Y (the Millennials) and Z which are known to have a shorter attention span and a strong preference for multitasking, using digital technology, social stimulation, and visual graphics when learning new materials** (G. Patel, 2017; Seemiller & Grace, 2016; Smith, 2012; Swanson, 2016). The 7-minute placebo response DVD lecture-oriented video may not have met these requirements. For example, subjects were not allowed to look at their cell phone while watching the video, but research has shown that Generation Y and Z respond to advertisements and gain knowledge when they are able to use three or more devices simultaneously that provide instance answers (D. Patel, 2017; Wotapka, 2017).
  - ➢ **Given the above generational learning preferences, it is recommended that a quick (one-minute) placebo response script that encourages discussion be explored as a placebo response educational tool.**
- **Post-Test IG females scored higher by 18 points than their male counterparts, although this difference was not significant (p=.27). Learning and cognitive style theories may also be applied to explain this finding. Males tend to prefer multimodal visual learning content compared to females** (Sinha et al., 2013; Wehrwein et al., 2007). The placebo response video was unimodal and auditory: approaches preferred by females. **Future tools aimed at enhancing males' learning of the key placebo response factors should take these learning styles into account.**
- Study limitations: (a) the study does not address whether subjects' increased knowledge about the placebo effect key factors translates to greater drug-placebo separation; and (b) it is unknown if subjects remember the placebo response key factors throughout their participation in trials (some sites have begun to read a script explaining these factors to each subject per study visit which should extend their understanding throughout the trial). Future studies should address these matters.

References attached to this poster handout.