A Subject-Targeted Placebo-Control Reminder Script: An In-Depth Empirical Exploration of How Subject Characteristics Moderate Placebo Response

Elan A. Cohen, Ph.D.[1], Howard H. Hassman, DO[1], David P. Walling, Ph.D.[2], Katarzyna Wyka, Ph.D.[3], Roberta R. Ball, DO[1], Jaclyn M. Lobb, MS[1], Dakota Hazzard-Randolph, MS[1], Ashok V. Joseph, MD[1], and Larry Ereshefsky, Pharm.D., BCPP[1,4]

HRI Science Division

Hassman Research Institute, Science Division[1]; Collaborative Neuroscience Network[2]; The City University of New York, Graduate School of Public Health and Health Policy[3]; Retired Professor, The University of Texas[4]

ABSTRACT

Introduction: With an increasing rate of clinical trials failing due to large placebo responses, researchers have investigated how subject characteristics (e.g., age, gender, body mass index or BMI) have impacted this response, with noteworthy inconsistent findings (Fraguas et al., 2018). A thorough review of the literature revealed no empirical investigation exploring how a subject-targeted intervention may control placebo response and how the response may vary based on subject characteristics. As such, this study adds important data to further our understanding about the relationship between subject intrapersonal variables and the placebo effect. **Methods:** In this US multicenter, single-blind, all placebo investigation, moderate to severe depressed patients (assessed by the self-reported Beck Depression Inventory-II / BDI-II; Beck et al., 1996) aged 18-65 were randomized to the Control Group (CG) or Intervention Group (IG). IG subjects were read the Placebo-Control Reminder Script (PCRS), educating them on the commonly cited key causes of the placebo effect, including participant expectations of benefit, lack of placebo understanding, misconception of expected interactions with research site staff, and subject role uncertainty (Rutherford & Roose, 2013). CG subjects were not read the PCRS. All subjects were informed of the 50% chance of being assigned placebo or active drug but received only placebo. Given this deception, subjects were provided a Debriefing Form at the end of the study revealing the investigation's true intent. **Results:** As expected, the IG (n=41) and CG (n=40) subjects did not differ in Baseline characteristics, including depression (BDI-II: IG M=33.80, SD=9.08 vs. CG M=31.10, SD=7.28; p=.144). A significant (p=0.018) time-by-group interaction, as hypothesized, indicated IG subjects reported significantly less improvement in BDI-II scores than CG subjects (IG M=26.10, SD=1.56 vs. CG M=20.68, SD=7.58). Post hoc subgroup analyses examined whether rate of change in BDI-II was different depending on subject characteristics. These stratified analyses were not powered to detect time-by-group interactions, and as such, between-group (IG vs. CG) effect sizes were computed for each subgroup at the end of the study. Analyses revealed that the PCRS tended to be more effective for females (d=.73), subjects who are under the age of 40 (d=.77), African-American (d=.66), have a high school degree or less (d=.59), have never been in a clinical trial (d=.73), have a normal BMI (d=1.04), currently in psychotherapy (d=1.43), presently not on psychotropic medication (d=.81), and have BDI-II scores at Baseline in the severe range as opposed to moderate (d=.62). **Conclusions:** The primary finding of the current study, that the PCRS helped manage the placebo effect among depressed subjects compared to those not read the PCRS, suggests that implementing this strategy within MDD RCT clinical trials may be crucial in managing this effect. Post hoc data also indicated that the PCRS may be particularly important in reducing the placebo effect for certain subjects. For example, many clinical trials have BMI restrictions and the current study results lend support for this exclusion and coincide with similar empirical findings (Talley et al., 2006) but counter others (Han et al., 2018) from a placebo response perspective. Implications of the subgroup findings to clinical trial placebo response, as well as study limitations, will be thoroughly discussed in the poster.

INTRODUCTION

- The importance of developing strategies that manage placebo response within psychiatric clinical trials cannot be understated. It is estimated that slightly over 50% of such trials fail because of poor active drug and placebo separation (Kirsch, 2016), including within major depressive disorder (MDD) double-blind, randomized, placebo-controlled trials (RCTs) (Khan et al., 2017). Further, the placebo effect has been found to be increasing over time (Kemp et al., 2010) with vital sequala impacting drug development costs, increased inconclusive and failed trials, delays in the development of new medications, and withholding potentially efficacious drugs to patients in need (Alphs et al., 2012).
- While various methodological strategies have been implemented or recommended to reduce the placebo effect (e.g., centralized ratings, remote rater monitoring, data surveillance before subject is randomized, subject duration of current illness exacerbation, and different lead-in phase procedures), **no subject targeted interventions aimed at reducing this phenomenon was found by the authors of this study to have been empirically investigated. This is surprising given the obvious role of study participants in producing the placebo effect.**
- Despite the lack of interventional research, there is general consensus (e.g., Alphs et al., 2012; Weber et al., 2005) about the subject-producing causes of the high placebo rate or what we term Placebo Response Factors (PRFs), including:
  - ❖ **Lack of subject understanding of the placebo**
  - ❖ **Subject expectations of benefit**
  - ❖ **Subject misconception of expected interactions with research site staff**
  - ❖ **Subject uncertainty of his/her role in the trial**
- Although Hassman et al. (2017a, 2017b) found that subjects can enhance their understanding about PRFs compared to study participants who were not educated about the factors, no research could be found that explored if such an understanding reduces the placebo effect.
- The current study is the first that these authors are aware of that specifically examines whether a Placebo-Control Reminder Script (PCRS; see **Figure 1**), which reviews the PRFs and read to subjects with major depression, decreases their response to placebo. Should the PCRS be empirically found to reduce the placebo effect compared to subjects who did not receive the PCRS, the current investigation also conducts a post-hoc analysis and examines if there are certain subject characteristics which may be more receptive to the education in which the PCRS provides.

METHODS

- This IRB approved study implemented a US multicenter (one site in the East and the other in the West Coast), randomized, single-blind, all placebo design aimed to mirror the methodologies typically used in MDD clinical trials, such as implementing conventional inclusion and exclusion criteria, multiple study visits, and evaluation of Adverse Events (AEs) and Serious Adverse Events (SAEs).
- Also similar to other MDD trials, subjects were informed via the Informed Consent Form they have a 50 percent chance of receiving active medication or a placebo. However, as part of the methodology of the current study, all participants received placebo.
  - ❖ Deception was necessary to assess for the placebo and nocebo effects and all subjects received a Debriefing Form at the end of their participation which revealed the true intent and procedures of the study.

METHODS (CONTINUED)

- The placebo was used as the Investigational Product (IP) because it allowed for specific measurement of the PCRS (the independent variable) to either decrease depression symptoms (the dependent variable) which would entail a placebo effect occurred, or help control for the placebo effect. The PCRS takes about 2 minutes to read and answer subject questions.
- The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used as the primary efficacy scale to assess depressive symptoms. Using this self-report scale was necessary given the single-blind design of the current study.
- Subjects digested the IP (total two white blinded placebo capsules at the Screening Visit and Visit 2) at the site rather than at home each day of the week in order to illuminate the risk that many clinical trials experience regarding study drug adherence at home (Shiovitz et al., 2016). To help rectify (equalize) the expectation by subjects of taking medication at home each day, subjects were informed the two active medication capsules were developed to sufficiently treat depressive symptoms.

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Male or female 18-65-years-old	Meets DSM-5 criteria for such disorders as schizophrenia, bipolar, schizoaffective, schizophreniform, dissociative disorder, intellectual disability, persistent depressive disorder, autistic disorder, dementia, and personality disorder (criteria for another DSM-5 psychiatric disorder may be met as long as the disorder is secondary to the MDE)
Current primary major depressive episode diagnosis (Recurrent or this be the subject's lifetime Single Episode)	No passive or active suicidal thoughts within 6 months of screening and no attempt within one year of screening
BDI-II Item #1 score of ≥ 1 AND total score ≥ 20 (representing at least a moderate depression level) AND Item #9 (Suicidal Thoughts or Wishes) score equal to 0 (no suicidal thoughts)	Initiated, terminated, or dose change of any psychiatric medication within 30 days of screening (subjects permitted to stay on such meds during study as long as no changes occurs during study participation)
The subject is outpatient with no hospitalization for worsening of any mental health symptoms within 6 months of the Screening Visit	Initiated, terminated, or changed psychosocial interventions within 6 weeks of screening (subjects permitted to maintain this intervention as long as no change occurs during study participation)
Good general medical health	Current or in past 6 months of screening meeting DSM-5 criteria for moderate to severe substance use disorder
Able to consent to study participation and able to comply with study protocol requirements	Females breastfeeding, lactating, or pregnant

The PCRS was placed here in the actual poster presented at ASCP.

The PCRS is a proprietary, licensed document.

If the reader would like a copy or discuss use of the PCRS in any research or clinical trial, they should contact:

Dr. Elan Cohen at ecohen@hritrials.com

Figure 1: Placebo-Control Reminder Script (PCRS) regarding PRFs which were read to all IG subjects at all study visits before the primary efficacy scale was administered.

RESULTS

- Eighty one subjects completed the study. The IG and CG subjects did not differ in any of the main characteristics (all p>.05) - see **Table 1** .
- As expected, there was no statistical difference in Baseline (Visit 1) BDI-II scores between the IG and CG subjects (IG M= 33.80, SD=9.08 vs. CG M= 31.10, SD=7.28, p=.144), as well as by gender, age, or race/ethnicity. **Figure 2** illustrates the results of the repeated measures two-way analysis of variance (ANOVA) whereby there was a significant time by group interaction of CG subjects showing marked decrease in BDI scores at Visit 3 compared to IG subjects (IG M=26.10, SD=1.56 vs. CG M=20.68, SD=7.58; p=0.018). **This mean decrease of 6-points may be statistically meaningful for MDD RCTs because achieving signal detection from placebo can be a matter of only a few point differences (e.g., 5) in the primary efficacy scale (Mallinckrodt et al., 2010; Mancini et al., 2014).**

RESULTS (CONTINUED)

- Effect sizes between IG and CG at Visit 3 were computed by dividing the model estimated between-group difference in BDI-II by common standard deviation of the change BDI-II scores from Visits 1 to Visit 3. These stratified post-hoc analyses revealed that the PCRS tended to be more effective for females, subjects under the age of 40, African-Americans, subjects who have a high school degree or less, never been in a clinical trial, have a normal BMI, currently in psychotherapy, presently not on psychotropic medication, and have BDI-II scores at Baseline in the severe range.– see **Figure 3**.

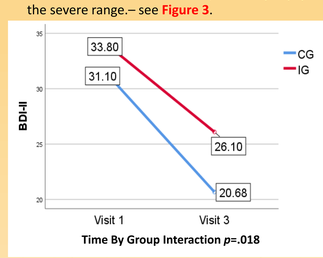
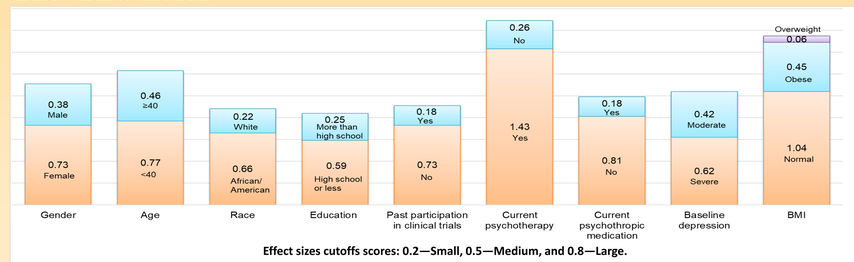


Figure 2: Change in BDI-II scores By group; results consistent across both US coast clinical trial sites.

Subjects Diagnosed as being in a Current Major Depressive Episode		
Characteristic	IG=41	CG=40
Age	M=44.27(SD=13.82)	M=44.05 (SD=14.66)
Age<40	13 (31.7%)	15 (37.5%)
Female	20 (48.8%)	23 (57.5%)
White/Caucasian	14 (34.2%)	15 (37.5%)
African/American	22 (53.7%)	21 (52.5%)
Other	5 (12.2%)	4 (10%)
Higher Education	13 (31.7%)	8 (20.0%)
Unemployed	33 (80.5%)	24 (61.5%)
Currently in psychotherapy	14 (34.1%)	10 (25.0%)
Currently on psychiatric med	21 (51.2%)	18 (45.0%)
Previously trial participation	12 (29.3%)	17 (42.5%)
Body Mass Index (BMI)	M=31.14 (SD=7.25)	M=32.40 (SD=8.37)

Table 1: Participant characteristics by group.



Figures 3: Effect sizes between IG and CG at Visit 3 with higher effect sizes representing subjects scoring higher on BDI-II (i.e., PCRS being more effective in controlling for the placebo effect).

CONCLUSIONS

- The current investigation is among the first, as far as the authors of this poster are aware, that explicitly examined an intervention developed specifically for subjects aimed to reduce the placebo effect. The results indicated that subjects with at least a moderate level of MDD symptoms reacted significantly less to receiving an inert substance and continued to exhibit clinical depressive symptoms when they were reminded of PRFs via the PCRS. Conversely, subjects who were not reminded of the PRFs had significantly decreased depressive symptoms(i.e., a significant placebo response).
- Post hoc subgroup analyses indicated that when examining distinct subject characteristics, certain subjects seemed to have less placebo response when read the PCRS compared to participants who were not read the script (i.e., the PCRS seemed to have helped control for the placebo response for certain subject attributes). Acknowledging the tentative nature of such analyses, the below discusses the arguably more intriguing and provocative findings:
  - ➢ **Comparing subjects who received the PCRS to those who were not read the script across the BMI sample spectrum, the PCRS seemed to benefit the normal BMI subjects (i.e., they had less placebo response) than the overweight and obese participants. Corroborating research has found that lower BMI is associated with lower placebo response (e.g., Talley et al.'s 2006 study on functional dyspepsia) but this contradicts other negative correlation findings between BMI and placebo response (Han et al.'s 2018 study on non-alcoholic fatty liver disease). Nonetheless, the PCRS results on BMI compliments the majority of psychiatric RCTs' exclusion criteria of higher BMIs.**
  - ➢ **The PCRS seemed to behoove African-American (AA) subjects more than their Caucasian counterparts. While there is no definitive research examining the relationship between race and the placebo effect, some evidence suggests that AA subjects are more likely to have a placebo response (Mulhall et al., 2018) but may be confounded by other variables such as BMI (Constantine et al., 2018). Despite these entangled findings, the PCRS may be pivotal in enhancing AA subjects' trust in the RCTs, especially since 50% of AAs report mistrusting clinical investigations (Research America, 2013) most likely derived from a deceitful research history (e.g., the Tuskegee Syphilis 1932-1972 experiments; Fisher & Kalbaugh, 2011).**
  - ➢ **Our results suggested that female subjects were more effected (i.e., had less placebo response) having had the PCRS read to them than male subjects. Enck and Klosterhalfen (2018) found that although there is no consistent relationship between gender and placebo effects within clinical trials, when experiments are conducted and conditioning / expectancy can be manipulated, slightly more studies find women to be placebo responders and, as such, a PCRS instrument may help control this generalized finding given our current study post hoc gender results.**
  - ➢ **Subjects under the age of 40 tended to obtain more of an advantage from the PCRS than older subjects. While, again, there are no consistent data relating age and placebo response, some studies (Mulhall et al., 2018) indicate that subjects under the age of 45 are more likely to have a placebo response. This suggests that if it was not for the PCRS, the ≤40 year-old subjects might have had an increased placebo effect.**
  - ➢ **The PCRS seemed be more effective for subjects in psychotherapy than those who were not currently receiving such support. These results are promising given that the former group could have potentially had a greater placebo effect because counseling could have helped decrease their MDD symptoms. The PCRS may have helped control for this confound. Many clinical trials permit subjects to continue ongoing therapy, and the PCRS may have important placebo response implications for such participants.**
  - ➢ **Research results have generally found that more severely depressed subjects have less placebo effect (Bialik et al., 1995), which corresponds with our finding that the higher depressed subjects (at Baseline) tended to benefit more from the education the PCRS provided than the less depressed participants.**
- Study limitations: Given that the post-hoc analyses were not powered to detect a statistically significant between-group differences, future investigations should enhance their sample size to determine the validity of our subgroup results. Additionally, the current investigation was not identical to MDD RCTs insofar as (a) the IP was provided to subjects once a week as opposed to every day; (b) there were three total visits rather than the more common 6-8 study visits; and (c) there was no active drug arm aimed to reduce MDD symptoms and, therefore, it is unknown how the PCRS might impact reporting of such symptoms if subjects were randomized to receive the compound (i.e., would the PCRS overly persuade subjects to report depressive symptoms?). These factors should be addressed in replicated studies, which would also serve to increase confidence in its findings.

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References provided on reverse side of poster handout.