A First-Time Investigation of a Subject Intervention to Reduce the Placebo and Nocebo Effects: A Multicenter, Randomized, Single-Blind, All Placebo Study of a Placebo-Control Reminder Script for Subjects with Major Depression

Elan A. Cohen, Ph.D.[1], Howard H. Hassman, DO[1], David P. Walling, Ph.D.[2], Steven Hoover, Ph.D.[2], Katarzyna Wyka, Ph.D.[3], Roberta R. Ball, DO[1], Ashok V. Joseph, MD[1], Jaclyn M. Lobb, MS[1], Dakota Hazzard-Randolph, MS[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: This investigation is the first known that empirically explores if educating subjects about key causes of the placebo effect significantly reduce placebo and nocebo effects. The key causes are Placebo Response Factors (PRFs), which include participant expectations of benefit, poor placebo understanding, misconception of expected interactions with site staff, and subject role uncertainty. **Methods:** In this Institutional Review Board approved, US multicenter, single-blind, all placebo investigation, moderate to severe depressed patients aged 18-65 were randomized to the Control Group (CG; n=40) or Intervention Group (IG; n=41). IG subjects were read the Placebo-Control Reminder Script (PCRS) which reviewed the PRFs before the primary efficacy scale (self-reported Beck Depression Inventory BDI-II) administration. CG subjects were not read the PCRS. Adverse Events were also collected to assess side effects. Subjects were informed of the 50% chance of being assigned placebo or active drug, yet all subjects received placebo. Given this deception, subjects were provided a Debriefing Form post-intervention revealing the investigation's true intent and procedures. **Results:** Subjects did not differ in baseline characteristics, including BDI-II scores (IG M=33.80, SD=9.08; CG M=31.10, SD=7.28, *p*=.144). A significant time-by-group interaction (*p*=0.018) indicated that IG subjects reported higher BDI-II scores post-intervention (IG M=26.10, SD=1.56; CG M=20.68, SD=7.58). Although not significantly different (*p*>.05), fewer IG subjects reported adverse events (IG 31.7%, CG 42.5%), improvement in depression (IG 36.6%, CG 52.5%), and belief they received real medication (IG 36.6%, CG 42.5%). **Conclusions:** The PCRS controlled the placebo but not the nocebo effect. Future investigation recommendations will be discussed.

INTRODUCTION

- The high rate of placebo effect, which is approximately 50% within major depressive disorder (MDD) double-blind, randomized, placebo-controlled trials (RCTs) (Khan et al., 2017), has been found to only be increasing over time (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, 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 the placebo or nocebo effect were found by the authors of this study to have been empirically investigated.
- 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**
- While 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 or nocebo effect.
- The current study is the first that these authors are aware of that 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 and reporting of side effects (i.e., lessens the nocebo effect).

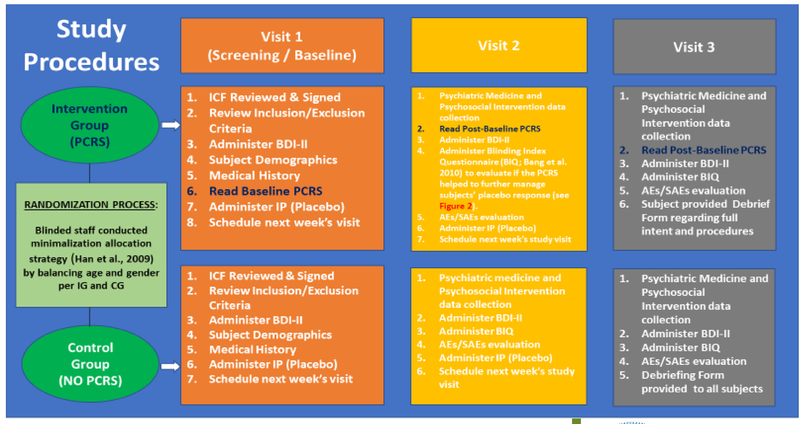
METHODS

- 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.
- 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.

METHODS (CONTINUED)

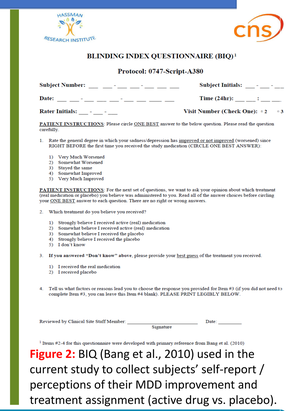
- Subjects digested the IP (total two white blinded placebo capsules at the Screening Visit and Visit 2) at the site rather than at home each day of the week in order to illuminate the risk that many clinical trials experience regarding study drug adherence at home (Shiovitz et al., 2016). To help rectify (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 CNS Summit.
The PCRS is a proprietary, licensed document.
If the reader would like a copy or discuss use of the PCRS, please contact:
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.


BLINDING INDEX QUESTIONNAIRE (BIQ)[1]

Protocol: 0747-Script-A380

Subject Number: ___ ___ ___ ___ ___ ___ Subject Initials: ___ ___ ___

Date: ___ ___ ___ ___ ___ ___ ___ ___ Time (24hr): ___ ___ : ___ ___

Rater Initials: ___ ___ ___ Visit Number (Check One): ☐ 2 ☐ 3

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

1. Rate the general degree as which your sadness/depression has improved or not improved (worsened) since RIGHT BEFORE the first time you received the study medication (CIRCLE ONE BEST ANSWER):
   1) Very Much Worsened
   2) Somewhat Worsened
   3) Stayed the same
   4) Somewhat Improved
   5) Very Much Improved

PATIENT INSTRUCTIONS: For the next set of questions, we want to ask your opinion about which treatment (real medications or placebo) you believe was administered to you. Read all of the answer choices before circling your ONE BEST answer to each question. There are not right or wrong answers.

2. Which treatment do you believe you received?
   1) Strongly believe I received active (real) medication
   2) Somewhat believe I received active (real) medication
   3) Somewhat believe I received the placebo
   4) Strongly believe I received the placebo
   5) I don't know

3. If you answered "Don't know" above, please provide your best guess of the treatment you received.
   1) I received the real medication
   2) I received placebo

4. Tell us what factors or reasons lead you to choose the response you provided for Item #3 (if you did not need to complete Item #3, you can leave this Item #4 blank). PLEASE PRINT LEGIBLY BELOW.

Reviewed by Clinical Site Staff Member _____ Date: _____
Signature

[1] Items #2-4 for this questionnaire were developed with primary reference from Bang et al. (2010)

Figure 2: BIQ (Bang et al., 2010) used in the current study to collect subjects' self-report / perceptions of their MDD improvement and treatment assignment (active drug vs. placebo).

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. Repeated measures two-way analysis of variance (ANOVA) indicated 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) – see **Figure 3**.

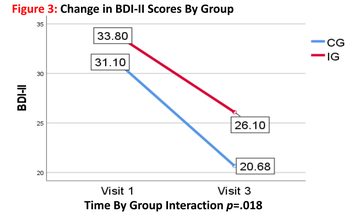
Subjects Diagnosed as being in a Current Major Depressive Episode		
Characteristic	**IG=41**	**CG=40**
Age	M=44.27 (SD=13.82)	M=44.05 (SD=14.66)
Age<40	13 (31.7%)	15 (37.5%)
Female	20 (48.8%)	23 (57.5%)
White/Caucasian	14 (34.2%)	15 (37.5%)
African/American	22 (53.7%)	21 (52.5%)
Other	5 (12.2%)	4 (10%)
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.

RESULTS (CONTINUED)

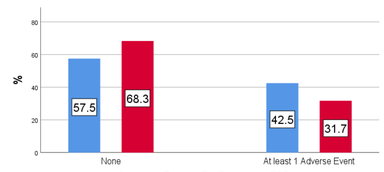
- As hypothesized, fewer IG subjects (31.7%) reported having at least one AE at either Visit 2 or Visit 3 compared to CG subjects (42.5%). Chi-squared analysis, though, indicated this difference was not statistically significant (*p*=.315) – see **Figure 4**. Also as expected, when examining only Visit 2, 8 IG subjects (19.5%) reported at least one AE vs. 16 CG subjects (40%) and this difference was statistically significant (*p*=.043). This significance disappeared at Visit 3: there were still 8 IG subjects (19.5%) who reported at least one AE but the CG decreased to 10 subjects (25%) (*p*=.553). Among subjects who reported AEs, the mean number in the IG was 2.07 (SD=1.75) compared to 2.59 (SD=1.50) in the CG (*p*=.409).
- As expected, IG subjects were less likely to report improvement in MDD symptoms (36.6%) compared to CG participants (52.5%). However, Chi-squared analysis indicated this difference was not statistically significant (p=.150) – see **Figure 5**.
- Per expectations, IG subjects (36.6%) were less likely to report being on real medication compared to CG subjects (42.5%). Chi-squared analysis, though, indicated this difference was not statistically significant (p=.150) – see **Figure 6**.
- The above findings were consistent in age groups (<40 & ≥40), gender, and race/ethnicities as well as across both research sites.

Figure 3: Change in BDI-II Scores By Group



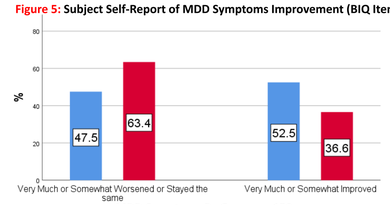
Time By Group Interaction *p*=.018

Figure 4: Adverse Events at Either Visit 2 or Visit 3 By Group



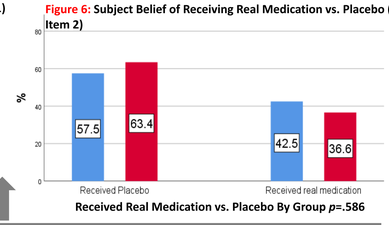
Adverse Events By Group *p*=.315

Figure 5: Subject Self-Report of MDD Symptoms Improvement (BIQ Item 1)



MDD Symptoms By Group *p*=.150

Figure 6: Subject Belief of Receiving Real Medication vs. Placebo (BIQ Item 2)



Received Real Medication vs. Placebo By Group *p*=.586

Study results consistent across both research sites

Figures 3-6 (above graphs): Comparisons between the IG and GC in BDI-II, AEs, and BIQ items

CONCLUSIONS

- Our thorough review of the literature revealed that the current study is the only one which empirically examines a direct intervention aimed at reducing the placebo effect. The current study results indicate that indeed the brief (approximate two minute) **PCRS is a key piece to the puzzle of how to significantly reduce the insidious placebo effect** within our industry, at least within MDD clinical trials. 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 the critical contents of the PCRS, including but not limited to the nature of a placebo, that site staff had no efficacy expectations and they too as study participants should have no expectations, and that subjects need to be honest regarding their symptoms. Conversely, subjects who were not reminded of these key placebo response factors significantly decreased in their reporting of depressive symptoms.
- Although no consistent AE data were statistically significant, meaningful trends were found. **Less subjects reported at least one AE at either Visit 2 or Visit 3 when reminded of the key placebo response factors** (i.e., experienced a reduced nocebo effect) as compared to subjects who were not read the PCRS, but this was not at a statistically significant level. On the other hand, by the time **subjects were read the PCRS at least twice, they were significantly less likely to report an AE at Visit 2** than their counterpart who were not read the PCRS, but this significance dissipated when less CG subjects reported AEs at Visit 3. It is possible that with increased visits in the investigation and an increase in *N*, a significantly lower number of IG subjects may have reported AEs.
  - ➢ Given the overall lack of a nocebo effect reduction in the IG subjects, it appears that the power of physically digesting a pill produces a strong perception of experiencing side effects – 66% of the AEs were reported immediately upon pill digestion, compared to 34% of the AEs experienced a day or more after the ingestion. This finding suggests that the **critical contents of the PCRS may need gradual internalization for controlling the nocebo effect**.
- While not being statistically significant, **subjects who were read the PCRS were more likely, as expected, to believe they received the placebo and reported their MDD symptoms felt the same or worsened since starting the study**. This data trend suggests an increase in subjects may produce a more statistically robust finding.
- The study results have **implications for MDD trials**, and arguably, perhaps also for other CNS study diagnoses such as Schizophrenia and PTSD. **Studies which implement the PCRS or its like may show significantly less placebo effects**, which can progress their compound to faster FDA approval and marketing that would reach patients sooner suffering from these ailments. We have IRB approval to apply the same research study to Schizophrenia and General Medical subjects, which we plan to initiate once funding is secured.
- Study limitations: although the goal was to duplicate typical MDD clinical trials, the current investigation was not identical to such studies 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, (c) the study compensation was $20 per visit and not the more typical $75, and (d) there was no independent Monitor reviewing sites' work (although each site had an independent staff member verifying the Excel spreadsheet entered data). These factors may have impacted the current study results and should be addressed in replicated studies, which would serve to increase confidence in its findings.

Poster presented at the Annual CNS Summit Meeting, November 2018, Boca Raton, FL

References provided on reverse side of poster handout.