Taming the Placebo Effect in Depression Clinical Trials: The Methodological Implementation of a Placebo-Control Reminder Script

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ABSTRACT

Introduction: Although the placebo effect continues to persist within depressive disorder double-blind, randomized, placebo-controlled trials (RCTs; Khan et al., 2017), no subject-targeted placebo reducing intervention within the RCT design has been investigated to reduce this effect. This is surprising since one of the primary sources of the placebo effect are RCT subjects. The current study is the first we know of that empirically explores if educating subjects about the key causes of the placebo effect or Placebo Response Factors (PRFs – participant expectations of benefit, lack of placebo understanding, misconception of expected interactions with research site staff, and subject role uncertainty; Weber et al., 2005) significantly reduces the placebo effect. **Methods:** In this US multicenter (one in the east and the other in the west coast), randomized, single-blind, all placebo investigation, patients aged 18-65 experiencing at least a moderate level of a major depressive episode per the self-reported Beck Depression Inventory-II [BDI-II; Beck et al., 1996) were randomly assigned to the Control Group (CG) or Intervention Group (IG). The IG were read at each of the three study visits a one-page, brief (2 minute) Placebo-Control Reminder Script (PCRS) reviewing the PRFs before the primary efficacy scale (BDI-II) was administered. CG subjects were not read the PCRS. The current investigation also deepened its assessment of the placebo effect by evaluating subjects' perceptions of their major depressive disorder (MDD) symptom improvement and which treatment they received. All subjects were informed via the Informed Consent Form there was a 50% chance of receiving placebo or active drug, but all subjects received placebo. Given this deception, subjects received a Debriefing Form at the end of the study revealing the investigation's true intent and procedures. **Results:** As expected, 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 that IG subjects reported significantly less improvement in BDI-II scores than CG participants post-intervention (IG M=26.10, SD=1.56 vs. CG M=20.68, SD=7.58). Although not significantly different, an expected trend was found with fewer IG subjects reporting improvement in their MDD symptoms (IG 36.6% vs. CG 52.5%, p=.150) and belief they received real medication (IG 36.6% vs. CG 42.5%, p=.586). Results were consistent across sites. **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. There are various methods the PCRS or similar script may be seamlessly applied, including but not limited to using the script as study source with instructions to raters within the script to read it before the primary efficacy scale is administered per participant and visit, while also having the rater initial, date, and document the time of the reading to relate to the efficacy scale administration. Other methods as well as study limitations will be discussed in the poster.

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 over 50% failure rate between psychiatric drugs and placebo (Kirsch, 2016), including within major depressive disorder (MDD) double-blind, randomized, placebo-controlled trials (RCTs) (Khan et al., 2017). Evidence also indicates the effect is only increasing as time progresses (Kemp et al., 2010) with systemic consequences involving significantly higher costs for drug development, 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
- 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 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.
- The current poster also provides recommendations of how the PCRS or similar script which reviews the PRFs can be seamlessly implemented in MDD clinical trials to enhance their methodology of reducing the placebo 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.

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 #9 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

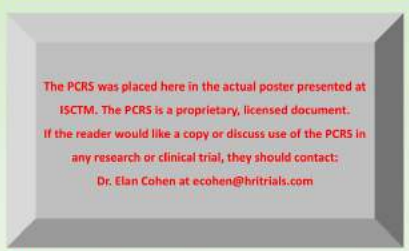

Figure 1: Placebo-Control Reminder Script (PCRS) regarding PRFs which were read to all IG subjects at all study visits before the primary efficacy scale was administered.

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. **Figure 3** 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)

- 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 4**.
- 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 5**.
- 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

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.

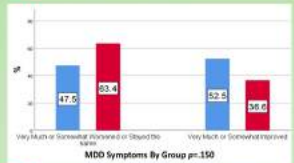

Figure 4: Percent of Subjects Reporting MDD Symptom Change (BIQ Item 1)

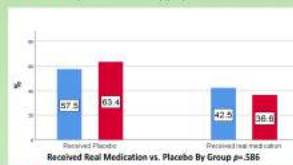

Figure 5: Percent of Subjects Reporting Belief in Receiving Real Medication vs. Placebo (BIQ Item 2)

Study results statistically consistent across both research sites

Figures 3-5 (above graphs): Comparisons between the IG and GC in BDI-II and BIQ items

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 indicate that the brief (approximate two minute) **PCRS may provide a key piece to the placebo effect puzzle which burdens our industry by significantly reducing this insidious effect**, at least within MDD clinical trials. Subjects in this study 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).
- 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.
- **Methodology Recommendations**: Should our results be replicated and considering the limitations of the study (see below), the following provides approaches of how the PCRS or any other similar script (which should contain the same information and elements within the PCRS) may be efficiently applied within the methodology of MDD clinical trials to facilitate reducing the placebo effect:
  - ➢ Using the PCRS, or its like, as paper source with the rater reading it to subjects at every study visit per subject before the primary efficacy measure is administered and this procedure is confirmed by the rater initial, dating, and indicating the time the PCRS was read.
  - ➢ Reading the script can be audio recorded and verified by a rater surveillance vendor who might typically already be listening to the quality of the primary efficacy assessment administration.
  - ➢ The script can be easily incorporated within the rater surveillance vendor's tablet and verified as having been read to subjects before administration of the primary efficacy scale.
  - ➢ The PCRS or a similar script may be implemented similarly as described above for other indications, depending on the results investigating the script for those disorders – we have IRB approval to apply the current research study design 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.

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References provided on reverse side of poster handout.