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 depression disorder double-blind, randomized, placebo-controlled trials (RCTs), Khan et al. (2017), 2017, no subject-focused placebo-reducing intervention within the RCT design has been investigatively analyzed. This is surprising since one of the primary sources of the placebo effect are RCT subjects. The current study is the first to know that empirically if educating about the known issues of the placebo effect (e.g., participant expectations of benefit, lack of understanding, misconception of expected interactions with research site staff, and subject role uncertainty; Weber et al., 2005) also significantly reduces the placebo effect. Methods: In the US (n=100) and the UK (n=97), 196 were randomised to the two (the UK) blinded, single-blind, all placebo-finished, patients aged 18-65 experiencing at least a moderate level of a major depressive episode per the self-reported Beck Depression Inventory (BDI II; Beck et al., 1961) 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 placebo’s potential impacts. The CG were given a Control Reminder Script (CRS). 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 medication, but all subjects reviewed 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 (M=32.40, SD=9.76) and CG (M=36.6, SD=9.05) did not differ in baseline characteristics. Depression (BDI II-scores vs CG patients post-intervention (IG M=13.10, SD=6.66, CG M=20.48, IG=6.78). 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<.05) andbelief they received real medication (IG 36.0% vs. CG 42.5%, p=.56). Results were consistent across both the current study and previous studies. 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 placebo studies is effective. The placebo effect. There are various methods the PCRS or similar script may be seamlessly applied, including not limited to using the script as source with instructions within the visit form to read it before the placebo efficacy scale is administered per patient and visit, and also before 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 posterior.

INTRODUCTION

The placebo effect’s profusion within the clinical trial industry can only be viewed as a plague with accompanying confounding consequences. This assertion stems from the slightly over 50% failure rate between psychotropic 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 potential efficacious drugs to patients in need (Alphs et al., 2014).

While various methodological strategies have been implemented or recommended to reduce the placebo effect (e.g., centralized ratings, remote rater monitoring, data surveillance before study visits, randomization of treatment administration, 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 instead giving 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. (2017, 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 confirming if such understanding reduces the placebo effect.

The current study is the first that these authors are aware of that examine 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 on how the PCRS or similar script which can be seamlessly applied, including not limited to using the script as source with instructions within the visit form to read it before the placebo efficacy scale is administered per patient and visit, and also before 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 posterior.

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% chance of receiving active medication or 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.

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 a statistical difference in Baseline (Visit 1) BDI II-scores between the IG and CG subjects (IG M=33.80, SD=9.28 vs CG M=31.30, SD=7.78, p=.144), and as 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 II-scores at Visit 3 compared to IG subjects (CG M=26.10, SD=12.56 vs IG M=20.48, SD=7.58, p=.038). This means decrease of 5.6 points may be statistically meaningful for MDD RCTs because achieving clinical detection from placebo can be a matter of only a few point differences (e.g., 5) in the primary efficacy scale (Matheson et al., 2016; Matheson et al., 2016).

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 (approximately seven minutes) placebo-controlled reminder script (PCRS) was a statistically significant, 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 displayed a statistically significant decrease in 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, 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 worse 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 scale is administered and this procedure is confirmed by the rater initial, date, 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 these 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.

References provided on reverse side of presenter handout.