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-controlled study, 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 reviewed. Results: IG 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=9.86; CG M=31.10, SD=7.28, p=.144). A significant time-by-group interaction (p=.018) indicated that IG subjects reported higher BDI-II scores past intervention (IG M=-10.60, SD=-20.68; CG M=-20.68, SD=-7.58; p=.000). Analyses: Results: IG results have implications for MDD clinical trials. Study procedures will be described. Conclusions: Further investigation will be recommended.

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., 2020).
• 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 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 of 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% chance of receiving active medication or a placebo. However, as part of the methodology of the current study, all participants received placebo.
• The placebo was used as the Investigational Product (IP) because it allowed for specific measurement of the placebo (an 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 Becks 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 given the single-blind design of the current study.

RESULTS

• Eighty-one subjects completed the study. The IG and CG subjects did not differ in any of the main characteristics (p>0.05; 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=9.86 vs. CG M=31.10, SD=7.28, p=0.144), as well as 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-II scores at Visit 2 compared to IG subjects (IG M=-10.60, SD=-20.68 vs. CG M=20.68, SD=7.58; p=0.018) – see Figure 3.

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References provided on reverse side of poster handout.