Can Subjects with Major Depression Learn About Key Placebo Response Factors: The Effect of an Educational Placebo Response Video

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Methodological Question Being Addressed: Can a brief video consisting of two doctorate-level individuals sitting in a chair, looking into the camera, and carefully teaching/reviewing the four key factors which are known in the clinical trial industry to induce placebo response in double-blind, randomized, placebo-controlled trials (factors are: misunderstanding of site-subject interactions, subject expectations of benefit, lack of subject understanding of placebo, and subject uncertainty of their role in the trial) help patients who are diagnosed with a current major depressive episode seeking to get into a depression clinical trial learn about these key factors, as opposed to patients who are not exposed to this teaching video?

Introduction: The challenge to reliably achieve signal detection in major depressive disorder (MDD) clinical trials cannot be overstated. MDD presents with the heaviest burden of disability among mental/behavioral disorders (NIH, 2017), yet less than 50% of double-blind, randomized, placebo-controlled trials (RCTs) demonstrate statistical superiority for active comparator drug over placebo (Khan et al., 2017). While researchers (Weber et al., 2005) have identified key factors which induce the placebo response (site-subject interactions, subject expectations of benefit, lack of subject understanding of placebo, and subject uncertainty of their role in the trial), the literature reveals few targeted methodological interventions which address the crucial Placebo Response Factors (PRFs). There are strategies addressing rater influence on placebo response (e.g., centralized raters), but they are not subject focused. MDD RCTs employing techniques aimed at educating subjects on PRFs can be additive to other strategies. **Methods:** MDD patients (N=64) participated in this pretest-posttest randomized-control group investigation. Subjects completed a Placebo Awareness Questionnaire (PAQ) containing 5 multiple choice questions to assess their awareness of the key PRFs. Upon completion of the PAQ, subjects were randomly assigned to the Control Group (CG) or Intervention Group (IG). The intervention was a seven-minute video educating subjects about the PRFs. Immediately after the IG subjects watched the video, they completed the same PAQ without access to their first responses. To match the temporality of the IG, the CG subjects completed the PAQ seven minutes after completing the first PAQ. **Results:** A repeated measures ANOVA showed a significant difference between the IG and the CG, demonstrating IG subjects were better able to identify the PRFs after watching the video ($p < .001$). Secondary analysis indicated this finding was true across age and gender (all $p < .05$ except for the 20-29 age group). Within-group analyses suggested a differential effect of the intervention on subgroups (e.g., IG females scored higher than IG males post video by 7 points) but not at a significant level. **Conclusions:** Despite MDE subjects prescreening for an RCT, these subjects could not identify PRFs. Subjects who watched a brief video had significantly greater awareness of these issues and their role in reducing placebo response as compared to subjects who did not watch the video. While a limitation of the study is that there were no outcome measures demonstrating improved signal detection, the current study results indicate that sponsors, research sites and rater training vendors should seriously consider implementing PRF training strategies for MDD subjects (e.g.,

the video used in this investigation or similarly purposed video) in order to potentially enhance signal detection and reduce placebo response. Learning style and attention theories may provide an explanation for why the 20- 29- year- old IG subgroup did not score significantly better than the CG of that same age group. It is recommended this study be replicated using other indications, evaluate the duration of improved understanding across study visits, and impact on placebo response.

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