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

Cohen, EA[1], Hassman, H[1], Walling, DP[2], Wyka, K[3], Ball, RR[1], Lobb, JM[1], Hazzard, D [1], Joseph, AV[1], Ereshefsky, L[1,2,4]

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]

Methodological Question Being Addressed: Can a one-page, brief Placebo-Control Reminder Script read to subjects reviewing factors known within the clinical trial industry to enhance the placebo response of study participants with Major Depression empirically reduce this effect, and if so, how might such a script be proficiently applied to double-blind clinical trials for this indication?

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.

Full Disclosure of Author Conflicts: All authors have no conflicts of interest or bias in the conclusions of the current investigation or promotion of the current study intervention. It is important to note that the authors of this study are not endorsing clinical trials to use the specific Placebo-Control Reminder Script investigated in the current study, but rather, with replicated findings, recommending that protocol developers seriously consider implementing a script which similarly educates subjects on the placebo response factors anecdotally discussed and empirically researched in the literature.

References:

Khan, A., Mar, K. F., Faucett, J., Schilling, S. K., & Brown, W. A. (2107). Has the rising placebo response impacted antidepressant clinical trial outcome? Data from the US Food and Drug Administration 1987-2013. World Psychiatry, 16, 181-192.

Weber, C., Kirby, L., McCarthy, C., Christensen, J., & Borwege, S. (2005). Reducing the placebo response: Triple blinding and setting expectations. Applied Clinical Trials (Online).