The Placebo-Control Reminder Script in Depression and Psychosis Trials: An Antidote for the Placebo and Nocebo Response

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ABSTRACT

Introduction: Depression and psychosis clinical trials share a crucial commonality of perpetually and alarmingly high placebo and nocebo responses (Rutherford et al., 2014; Rief et al., 2009). At ASCP in May 2019, Cohen et al. (2019) presented data indicating that the Placebo-Control Reminder Script (PCRS) significantly reduced the placebo effect among subjects in a major depressive episode (MDE). Since then, the same study design, including the dependent variable of depressive symptoms, was applied among subjects with a psychotic disorder. The current poster presents these data and the combined results from both populations with the goal of having a deeper understanding of the potential impact the PCRS has in mitigating these phenomena. **Methods:** Across two US sites, schizophrenia / schizoaffective adult patients experiencing at least moderate depression as determine by the self-reported Beck Depression Inventory-II (BDI-II; Beck et al., 1996), were randomized into two groups. The Intervention Group (IG) was read the one-page, brief (2 minute) PCRS before administering the BDI-II. The Control Group (CG) was not read the PCRS. The script reviews key Placebo Response Factors known in the clinical trial industry to induce placebo and nocebo effects (e.g., participant and site expectations of benefit; Alphs et al., 2012). Depression, and not psychosis, was selected as the dependent variable due to a combination of scale psychometric limitations (e.g., the lack of targeted self-report psychosis measures) and administration duration. The BDI-II, Adverse Events (AEs), and subjective beliefs about treatment were collected at the baseline, one-week mid-point, and two-week end-point visits. All subjects were informed via the Informed Consent Form that there was a 50% chance of receiving placebo or active drug aimed to improve their depression, 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 hypothesized, data from the combined MDE and psychosis sample indicated that the IG (n=70) reported significantly smaller decreases in BDI scores than the CG (n=67) across study visits (visit-by-group interaction: F[1,124]=9.81, p<.005). The proportion of patients that reported AEs at Visit 2 was significantly smaller in the IG than the CG (X^2=5.04, p<.05), though the groups did not differ at Visit 3 (X^2=1.52, p>0.05). As expected, a significantly higher proportion in the IG perceived they had an overall improvement in depressive symptoms than the CG (X^2=6.76, p < .01), but surprisingly, the groups did not differ in the proportions believing they were in the active medication versus placebo condition (X^2=1.39, p>.05). The results were similar in the psychosis sample, except that the IG (n=25) and CG (n=25) subjects did not differ in reporting AEs at Visit 2, though the CG reported a trend toward higher AEs at Visit 3 (p=.07). **Conclusions:** The combined data, along with the separate psychosis sample analysis, indicate that the PCRS is a powerful tool in managing the placebo effect within clinical trials. Given that the IG combined sample scored approximately 5.0 BDI-II points higher (i.e., less placebo response) than the CG at Visit 3, the PCRS has the potential to increase the effect size in placebo-controlled clinical trials in either indication. The PCRS has been positively implemented in such studies, which the poster will review. Current study limitations (e.g., 3 study visits as opposed to having more, which is typical for clinical trials) and future work (e.g., investigating the impact of the script on neurological indications, such as migraines) will also be described in the poster.

INTRODUCTION

- Given the perpetual and alarmingly high placebo and nocebo responses within these MDD and psychosis trials (Rutherford et al., 2014; Rief et al., 2009), it is crucial to focus on developing interventions to reduce these phenomena.
- Various methodological approaches have been implemented or recommended (e.g., centralized ratings and data surveillance before subjects are randomized) to manage these responses, but the authors of this poster know of **only one subject-targeted intervention, the Placebo-Control Reminder Script (PCRS), which has been empirically validated within an MDD sample to reduce these phenomena which was presented at ASCP in 2019 (Cohen et al., 2019).**
- The PCRS reminds both subjects and raters about Placebo Response Factors (PRFs) commonly cited in our clinical trial industry as producing placebo and nocebo effects (e.g., Alphs et al., 2012; Weber et al., 2005):
  - ❖ **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**
- The current investigation explored whether the PCRS reduces the placebo and nocebo effects among subjects with a psychotic disorder and not just subjects with MDD. The current poster also presents data that combines the PCRS previous Cohen et al. (2019) MDD data with the new psychosis sample to determine the extent to which the script mitigates the placebo and nocebo responses.

METHODS

- Two sites (one site in the East and the other in the West Coast) enrolled for this randomized, single-blind, all placebo study.
- The Informed Consent Form stated participants have a 50% chance of receiving active medication or a placebo. However, as part of the purposeful methodology of the current study, all participants received placebo.
- The placebo was used as the Investigational Product (IP) because it allowed the study to measure the extent to which the PCRS (the independent variable; see **Figure 1**) could maintain depressive symptoms (the dependent variable).
- The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used as the primary efficacy scale completed at all study visits.
- The Blinding Index Questionnaire (BIQ; Bang et al., 2010; see **Figure 2**) was completed at Visits 2 and 3 to assess subjects' perceptions of degree of improvement and which medication (active or placebo) they were taking.
- Depression, as opposed to psychotic symptoms, was selected as the dependent variable in the psychosis sample because only two widely used self-reported scales assess psychosis (the Brief Symptom Inventory and Symptom Checklist 90 Revised), but only do so validly and reliably by evaluating other general mental health factors which were not relevant to the purposes of the current study. Moreover, using either of the scales would add significant duration and possible frustration on behalf of the subjects when completing the primary efficacy scale.
- Three total study visits: Screening where in this study they received the IP and two more study visits separated by one week apart.
- Subjects digested the IP at the site rather than at home each day of the week in order to illiminate the risk that many clinical trials experience regarding study drug adherence at home (Shiovitz et al., 2016).

METHODS (CONTINUED)

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Male or female 18-65-years-old	Meets DSM-5 criteria for such disorders as Bipolar, 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)
Currently experiencing a MDE per the DSM-5	Current or in past 6 months of screening meeting DSM-5 criteria for moderate to severe substance use disorder
Have a current primary diagnosis of Schizophrenia or Schizoaffective (Bipolar or Depressive Type) Disorder. Subjects in the MDD sample were required to ONLY have a MDD diagnosis and NOT these psychotic disorders.	No passive or active suicidal thoughts within 6 months of screening and no attempt within one year of screening. No BDI-II Item #9 (Suicidal Thoughts of Wishes) ≥ 1 at screening (a score of 1 = "I have thoughts of killing myself, but I would not carry them out).
Be on at least one antipsychotic medication at the same dose ≥ 30 days from screening and agree to continue this same medication(s) and dose throughout study participation (N/A to the MDD sample)	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)
BDI-II Item #1 score of ≥ 1 ("I feel sad much of the time") 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 changed psychosocial interventions within 6 weeks of screening (subjects permitted to maintain this intervention as long as no change 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	Females breastfeeding, lactating, or pregnant
Able to consent to study participation and able to comply with study protocol requirements	

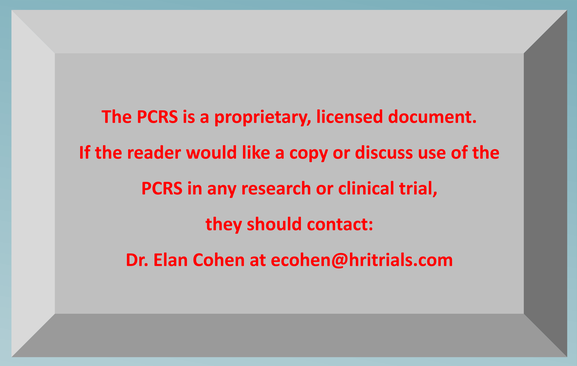
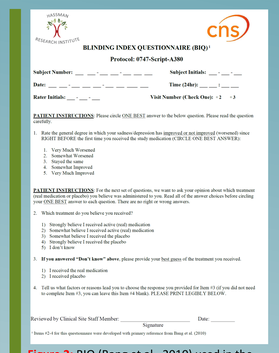


Figure 1: Placebo-Control Reminder Script (PCRS) which reviews PRFs read to all IG subjects at all study visits before the primary efficacy scale was administered.


BLINDING INDEX QUESTIONNAIRE (BIQ)[1]
Protocol: 0747-Script-A380

Subject Number: ___ ___ ___ ___ ___ ___ ___ Subject Initials: ___ ___ ___
Date: ___ ___ ___ ___ ___ ___ ___ ___ Time (24hr): ___ ___ ___ ___
Rater Initials: ___ ___ ___ Visit Number (Check One): ☐ 2 ☐ 3

PATIENT INSTRUCTIONS: Please circle ONE BEST answer to the below question. Please read the question carefully.

1. Rate the general degree in which your sadness-depression has improved or not improved (worsened) since RIGHT BEFORE the first time you received the study medication (CIRCLE ONE BEST ANSWER):
   1. Very Much Worsened
   2. Somewhat Worsened
   3. Stayed the same
   4. Somewhat Improved
   5. Very Much Improved

PATIENT INSTRUCTIONS: For the next set of questions, we want to ask your opinion about which treatment (real medication or placebo) you believe was administered to you. Read all of the answer choices before circling your ONE BEST answer to each question. There are no right or wrong answers.

2. Which treatment do you believe you received?
   1) Strongly believe I received active (real) medication
   2) Somewhat believe I received active (real) medication
   3) Somewhat believe I received the placebo
   4) Strongly believe I received the placebo
   5) I don't know
3. **If you answered "Don't know" above**, please provide your best guess of the treatment you received.
   1) I received the real medication
   2) I received placebo
4. Tell us what factors or reasons lead you to choose the response you provided for Item #3 (if you did not need to complete Item #3, you can leave this Item #4 blank). PLEASE PRINT LEGIBLY BELOW.

Reviewed by Clinical Site Staff Member: _____ Date: _____
Signature

* Items #2-4 for this questionnaire were developed with primary reference from Bang et al. (2010)

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

COMBINED MDD AND PSYCHOSIS SAMPLE:

- 137 subjects completed Visit 3 and their data were analyzed for all three visits (i.e., not just comparing the Baseline and Primary Efficacy visits), with 70 participants randomly assigned to the IG and 67 to the CG. **Table 1** lists the subjects' demographics by group.
- The IG and CG subjects did not significantly differ in baseline characteristics, including the primary demographics such as sex or race and by BDI-II scores (IG M=30.24, SD=8.52 vs. CG M=28.60, SD=6.84, p=.22).
- As hypothesized, per a Repeated-Measures ANOVA, results indicated that the IG reported significantly smaller decreases in BDI scores than the CG at the pre-identified primary efficacy Visit 3 (visit-by-group interaction: F[1,124]=9.81, p<.005; see **Figure 3**).
- The proportion of patients that reported AEs at Visit 2 was significantly smaller in the IG than the CG (X^2=5.04, p<.05), though the groups did not differ at Visit 3 (X^2=1.52, p>0.05; see **Figure 4**).
- As expected, a significantly higher proportion in the IG perceived they had an overall improvement in depressive symptoms than the CG (X^2=6.76, p < .01; see **Figure 5**), but surprisingly, the groups did not differ in the proportions believing they were in the active medication versus placebo condition (X^2=1.39, p>.05; see **Figure 6**).

PSYCHOSIS SAMPLE:

- To determine if the PCRS has merit in reducing placebo and nocebo response within the psychosis sample alone, data were analyzed without the MDD sample using the same statistical procedures as was conducted among the combined sample.
- 23 psychosis subjects were randomly assigned to the IG and 23 to the CG, with no difference in either groups' baseline characteristics, including BDI-II scores (IG M=24.70, SD=3.54 vs. CG M= 24.40, SD=3.26, p=.748) and diagnosis of either Schizophrenia or Schizoaffective Disorder (all p>.05) - see **Table 1** .
- BDI scores showed a significantly smaller decrease across visits in the IG than the CG (visit-by-group interaction, (F[1,78] = 10.61, p<.005).
- The groups did not differ in the proportions reporting AEs at Visit 2 or Visit 3 (p>.05).
- Regarding subjective beliefs, a significantly higher proportion in the CG self-perceived they had an overall improvement in depressive symptoms than the CG (X^2 [1, N=46] = 6.13, p<.05), with a non-significant trend (X^2 [1, N=46] = 4.46, p>.05) of the IG believing their symptoms worsened or stayed the same compared to the CG. However, when looking at the psychosis sample alone, a Chi-Squared test revealed a significantly larger proportion of the IG believed they were worse or the same regarding their depressive symptoms (IG 82.6% vs. CG 47.8%, p=.013).
- No significant IG and CG differences were found in the proportions believing they were in the active medication vs. placebo condition).
- All of the above results were consistent across the two research site locations.

Combined Sample		
Characteristic	IG = 70	CG = 67
Age	M=46.43(SD=12.53)	M=46.48 (SD=13.58)
Male	39 (55.7%)	21 (31.3%)
White/Caucasian	18 (25.4%)	21 (31.4%)
African-American	44 (63.8%)	39 (58.2%)
Other Race	8 (11.7%)	7 (10.4%)
Education: Secondary (high school) or less	56 (80.0%)	55 (82.1%)
Unemployed	60 (85.7%)	50 (74.6%)
Currently in psychotherapy	19 (27.1%)	13 (19.4%)
Number previous trials (range was 0-14)	1.41 (2.42)	1.81 (3.00)
Body Mass Index (BMI)	M=31.51 (SD=7.23)	M=31.88 (SD=8.19)
Major Depressive Disorder	43 (61.4%)	42 (62.7%)
Schizophrenia / Schizoaffective Disorder	20/25 / 7/25 (38.6%)	17/25 / 8/25 (37.3%)

Table 1: Participant (for the combined sample) characteristics by group

Figure 3: Change in BDI-II scores by group in combined sample; results consistent across both US coast clinical trial sites

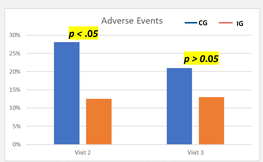


Figure 4: Subjects' report of AEs by group

Figure 5: Subjects' reported perceptions of improvement level by group

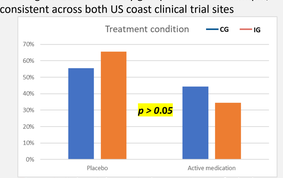


Figure 6: Subjects' reported perceptions of which medication they were randomly assigned by group

CONCLUSIONS

PLACEBO EFFECT:

- The results of the current investigation indicate that continuous reminding of PRFs via the PCRS has powerful implications toward mitigating the placebo effect in MDD and psychosis study participants.
- The PCRS may be a powerful tool to enhance the effect size within such trials – participants who received the PCRS on average scored 5-points less on the primary outcome measure than those who did not have such access and this 5-point difference in a primary outcome measure can be vital in boosting the required statistically significant separation between active drug and placebo with such study subjects (Mallinckrodt et al., 2010; Mancini et al., 2014).
- The **PCRS is simple to implement within clinical trials – it has a short administration time (approximately 2-3 minutes total), uses uncomplicated language, and is streamlined procedurally**.
- The PCRS has been seamlessly implemented in placebo-controlled clinical trials and with positive results. Noven Pharmaceuticals conducted a Phase 3, 6-week acute inpatient Schizophrenia trial which showed statistically significant separation of their HP-3070 (Asenapine patch) from placebo, resulting in FDA approval. Noven fortunately shared the unblinded data post study completion with Hassman Research Institute (HRI), which administered the PCRS to their participant cohort. HRI was the highest US study enroller and 4th highest globally. While HRI's data could not be analyzed for significance given the low n, the site's 15.3 average point difference (see **Figure 6**) between HP-3070 and placebo at week six suggests that the PCRS may be a contributing factor to the site's data and that the active medication group was not negatively impacted by the PCRS (see below Study Limitations Section). To confirm this in placebo-controlled trials, it would be ideal for future studies to include a PCRS and non-PCRS group or have an accumulation of such trials using the PCRS or similar script showing significant separation between the study compound and placebo.

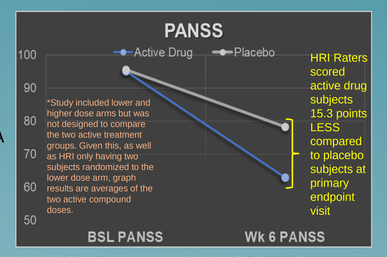


Figure 6: Site data on an acute inpatient Schizophrenia placebo-control investigation (Noven Pharmaceuticals) having administered the PCRS to all study site subjects immediately before all PANSS administrations.

- Also as expected, **subjects who received the PCRS were significantly more likely to report not improving regarding their depressive symptoms and those who did not receive the script reported feeling better**. These findings are not surprising given that subjects who did not have PCRS access had a significantly higher placebo response.
- The current data indicated there was no significant difference between subjects who were or were not read the PCRS regarding their belief of which treatment (active medication versus placebo) they received. This was surprising since the results showed that the IG subjects remained more depressed and they perceived their depressive symptoms as not improving – so why would these subjects also not report suspecting they were provided placebo? Surely the IG subjects were aware of what a placebo is since the PCRS explains this. One of the scales completed by all study participants, the BIQ (see Figure 2), assessed qualitative data regarding their beliefs about which treatment they received. Analyzing these data may provide insight into this specific finding.

NOCEBO EFFECT:

- The PCRS significantly helped manage the reporting of AEs at the second study visit. While this trend continued at the third visit, it was not significant. This was surprising since the contents of the PCRS are intended to be accumulatively learned. A potential explanation for the Visit 3 finding may simply be the lack of reported AEs in both the CG and IG at this specific visit. Future research should extend study visits beyond the current three to help determine the impact of the PCRS on the nocebo effect.
- Nonetheless, the results in the current study are promising as they indicate the PCRS not only helped manage the placebo effect, but also showed a trend toward mitigating the nocebo effect. Reducing this phenomenon in clinical trials is crucial in helping to increase subjects' drug compliance and decrease their leaving the study early, as well as unnecessarily halting the compound research program (Barsky et al., 2002; Faase & Petrie, 2013; Myers et al., 1987; Preston et al., 2000).

STUDY LIMITATIONS:

- Although the goal was to duplicate typical 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, subsequently, it is unsure if subjects would have reported depressive symptoms differently with higher compensation, (d) it is unsure if the results for the dependent variable (depressive symptoms) transfer to psychotic symptoms, and (e) while the above Noven data begins to address this matter, there was no active drug arm in the current investigation that aimed to reduce MDD symptoms and, therefore, it is unknown how the PCRS would have impacted these assigned subjects' reporting of depressive symptoms (i.e., would the PCRS influence active medication subjects' reporting of depressive symptoms?). These factors may have impacted the current study results and should be addressed in future studies.

References provided on reverse side of poster handout.

Poster presented at the Annual Meeting of the
American Society of Clinical Psychopharmacology (ASCP), May 2020, Miami, FL